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THE PHARMACOLOGY OF ANTICOAGULANT AGENTS*

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The anticoagulants of current interest in the management of thrombosis and embolism are heparin and dicumarol. It is the purpose of this brief review to present the important aspects of their chemistry and pharmacologic actions. More detailed discussions may be found in the reviews of Quick[1] and of Prandoni and Wright[2] which have appeared within the past few years.

HEPARIN

Thirty-three years have elapsed since McLean[3] extracted an anticoagulant from liver to which the name heparin was applied by Howell and Holt[4] in 1918. In the intervening time our knowledge of this substance has gradually developed. It is, however, still incomplete due, in part at least, to controversies which still exist regarding the details of the normal clotting mechanism.

Chemistry: Heparin is a complex organic polymer, the exact structure of which has not been established. As a result of the work of Jorpes and Bergström[5] and of Charles and Todd[6] it is known to have the structure of a mucoitin polysulfuric acid. In more detail, the factor contains a basic tetrasaccharide unit consisting of two molecules of acetylated glucosamine and two molecules of glycuronic acid. This tetrasaccharide is esterified with possibly a variable number of sulfuric acid groups resulting in a strongly acidic and electronegative compound which has the property of forming stable salts with proteins. It has been suggested that this property offers an explanation for its actions in that it may modify the actions of the protein enzymes concerned in the coagulation of blood. This property also leads to its binding and inactivation by highly basic proteins such as protamine. The possibility exists that heparin is not a single chemical entity but may be a mixture of closely related compounds. This might explain the difference in potencies of heparins isolated from various species.[7] Stable sodium and barium salts of heparin are readily prepared.

Action: Heparin in itself is only weakly, if at all, anticoagulant, as may be demonstrated on purified clotting factors of blood[8, 9] In the presence, however, of a cofactor of normal plasma or serum, heparin is a powerful anticoagulant. This cofactor, although still not definitely identified, is in the most soluble of the serum albumin fractions. Apparently it is possible for heparin to act at two stages of the clotting process. It was originally described by Howell and Holt[4] as an antiprothrombin. This property has been confirmed by Brinkhous and co-workers.[9] In other words, it prevents the formation of thrombin from prothrombin. The exact mechanism of this

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action is still problematic, although Quick[1] is strongly of the opinion that it does not counteract the action of thromboplastin. Heparin is also an antithrombic agent in the presence of a normal cofactor of serum.[10] There is considerable evidence that this co-factor may be the normal antithrombin the action of which is catalyzed by heparin.[1]

The anticoagulant action of heparin is rapid and is transitory. An intravenous injection of a single dose sufficient to prolong the coagulation time to thirty minutes has a latent period of only a few minutes and the action wears off in from two to three hours. A minor portion is excreted in the urine[11] but most of it is unaccounted for, possibly being destroyed by an enzyme heparinase which has been found in body tissues.[12]

A number of secondary actions of heparin may be briefly mentioned. It inhibits the agglutination of platelets and the accumulation of white thrombi both in vitro and in vivo. This may be an important action in preventing the beginning of thrombus formation.[13] It also increases the resistance of erythrocytes to hypotonic salt solutions and inhibits the action of complement. Consequently, its presence may be a disturbing factor in fragility tests and in certain serological reactions.

Physiological Significance: Heparin is presumably produced by the mast cells of Ehrlich found in the connective tissue surrounding the blood vessels, being particularly abundant in the vena cava. The lungs, liver, and cornea are rich in mast cells, and other tissues contain them in varying amounts. The evidence for this site of formation is as follows. A characteristic staining reaction given by heparin with toluidine blue is also given by the granules of the mast cells with this dye. It is also of interest that in a number of tissues a parallelism exists in the abundance of mast cells, the crude heparin content, and the concentration of ester sulfates. The stores of extractable heparin, particularly in the lungs and liver, suggest that it has a pysiological function, but this has not been established. In certain abnormal states, however, increased amounts of heparin have been demonstrated in the blood. In peptone and anaphylactic shock, heparin is released into the blood stream decreasing the coagulability of the blood as demonstrated by Jaques and Waters in dogs.[14] An interesting corollary to this is the fact that heparin inhibits in vitro the release of histamine from blood cells to plasma caused by trypsin, proteose or a specific antigen[15] An increase in the heparin content of the blood also results from ionizing irradiation[16] and by nitrogen mustard,[17] as shown by Allen and his colleagues. There is, however, much to be learned concerning the significance of these observations.

Heparin for clinical use is prepared from lung or liver tissue. It is available as a solution of the sodium salt in sterile 10 cc. ampules containing 10 mg. per cc. and of a potency not less than 100 units per mg. of the dry material. Heparin may be sterilized by boiling or by autoclaving at 110° C. for not over thirty minutes. Sterile solutions in ampules keep indefinitely. It is inactive when administered orally. The above aqueous preparations are administered intravenously. Certain preparations have been prepared in special menstruums for subcutaneous[18] and for intramuscular[19] injection.

For the purposes of assay or standardization, a pure preparation of the barium salt of heparin prepared by the Toronto group has been used, to which a potency of 100 units per mg. was assigned. This unit is approximately five times as large as the original Howell unit. There is now available a provisional international standard of the sodium salt of heparin of a potency of 130 units per mg. Several methods are available by which the commercial preparations may be assayed by comparison with the standard.

DICUMAROL

The story of the development of our knowledge of dicumarol is a familiar one. A hemorrhagic disease in cattle resulting from the eating of spoiled sweet clover was described by Schofield[20] over twenty-five years ago. Roderick[21] in 1931 made an important contribution by showing that prothrombin was the deficient coagulation factor in this condition. This point was confirmed ten years later by Link and his associates who proceeded to isolate and crystallize the hemorrhagic agent[22] and then to identify it chemically and to synthesize it.[23] Since that time the compound has been available for clinical use.

Chemistry: Dicumarol is a white or slightly buff colored crystalline solid, practically insoluble in water but forming soluble salts with alkalis. Chemically it is 3,3′ methylene-bis-(4-hydroxycoumarin). Coumarin itself is a compound widely distributed in the vegetable kingdom. When fused with potassium each molecule of dicumarol yields two molecules of salicylic acid.

Administration and Metabolism: Due to its low solubility in water except in alkaline solution it is not well suited for parenteral injection. It is, however, well absorbed on oral administration, although at a rather slow rate[24] and apparently is absorbed to some extent when administered by rectum.[25] In the plasma it is almost completely bound by protein and is bound to a high degree in the tissues. It is slowly metabolized and only traces appear as such in the urine.[24]

Action: As previously stated, dicumarol impairs the clotting mechanism by reducing the prothrombin content of the blood. Apparently it does not destroy prothrombin since unlike heparin it is inactive in vitro. The evidence points to an inhibition of the synthesis of prothrombin by the liver possibly by an interference with the utilization of vitamin K[1]. It is also known that massive doses of vitamin K or its analogues are at least partially effective in counteracting the action of dicumarol. Quick[1] believes that prothrombin consists of an unstable component A linked by calcium with a stable component B, and it is the latter stable component which is decreased by dicumarol. This opinion has been disputed.[26, 27] More recently MacMillan[28] has presented evidence suggesting that the decrease in prothrombin produced by dicumarol is only apparent and that it is a prothrombin accelerator which is deficient.

In any case, dicumarol administration causes a fall in the prothrombin activity of the blood. The prothrombin time which is used to measure the dicumarol effect increases only slowly until the prothrombin activity decreases to approximately 30 per cent of normal. It then begins to increase at a much more rapid rate.

Unlike heparin, dicumarol produces a slow but persistent response. There is a latent period of at least twelve to twenty-four hours. Complete action is evident over the course of three to four days after administration, following which it gradually declines. This is in keeping with the mechanism of action of the drug. After it blocks the formation of prothrombin in the liver the blood content must be gradually depleted. A critical minimum dose is necessary to produce a marked effect but greatly increasing the dose above this value will not hasten the result.[1] Following the action of dicumarol on the liver, that organ must restore the blood prothrombin before normal coagulation is possible. In contrast, heparin which acts on the clotting mechanism in the blood, acts almost at once, and since it is quickly destroyed and excreted the action is evanescent.

Like heparin, dicumarol has been reported to inhibit platelet adhesiveness[29] which may be an additional beneficial action in the prevention of thrombosis.

Toxicity: The danger from dicumarol as used clinically is limited to hemorrhagic manifestations. Apparently the action on the liver is specifically against prothrombin production since liver function tests have shown no impairment to that organ in clinical cases nor has liver injury been found in animals at autopsy after moderate doses. It has been reported, however, that patients

with cirrhosis of the liver and rats with liver injury due to carbon tetrachloride show increased sensitivity to dicumarol.[1] With large repeated doses resulting in death, central necrosis of the liver was frequently found in rats and occasionally in rabbits, mice and dogs.[30] Acute lethal doses in animals are of the order of 40 mg. per kg. Dogs die in circulatory collapse without hypoprothrombinemia. Hyperglycemia and a rise in metabolic rate and rectal temperature occur.[31] Capillary dilatation after large doses in animals has been observed by several investigators. Such findings, however, from the standpoint of dosage, hardly apply to the clinical use of the drug where the main concern is to produce a limited hypoprothrombinemia.

REFERENCES

Heparin

1. Quick, Armand, J.: Physiol. Rev., 24:297, 1944.
2. Prandoni, A. and Wright, I.: Bull. New York Acad. Med., 18:433, 1942.
3. McLean, J.: Am. J. Physiol., 41:250, 1916.
4. Howell, W. H. and Holt, E.: Am. J. Physiol., 47:328, 1918.
5. Jorpes, E. and Bergström, S.: J. Biol. Chem., 118:447, 1937.
6. Charles, A. F. and Todd, A. R.: Biochem. J., 34:112, 1940.
7. Jaques, L. B., Waters, E. T. and Charles, A. F.: J. Biol. Chem., 144:229, 1942.
8. Quick, A. J.: Proc. Soc. Exper. Biol. & Med., 35:391, 1936.
9. Brinkhous, K. M., Smith, H. P., Warner, E. D. and Seegers, W. N.: Am. J. Physiol., 125:683, 1939.
10. Quick, A. J.: Am. J. Physiol., 123:719, 1938.
11. Copley, A. L. and Schnedorf, J. G.: Am. J. Physiol., 133:562, 1941.
12. Jaques, L. B.: J. Biol. Chem., 133:445, 1940.
13. Best, C. H., Cowan, C. and McLean, D. L.: J. Physiol., 92:20, 1938.
14. Jaques, L. B. and Waters, E. T.: J. Physiol., 99:454, 1941.
15. Dragstedt, C. A., Wells, J. A. and Rocha e Silva, M. Proc. Soc. Exper. Biol. and Med., 51:191, 1942.
16. Allen, J. Garrott and Jacobson, L. O.: Science, 105:388, 1947.
17. Smith, T. R., Jacobson, L. O., Spurr, C. L., Allen, J. G. and Block, M. H.: Science, 107:174, 1948.
18. Loewe, Leo, Rosenblatt, Philip and Hirsch, Edward: J. A. M. A., 130:386, 1946. Loewe, Leo. Am. J. Med., 3:447, 1947.
19. Vorzimer, Jefferson J., Sussman, Leon H. and Marder, Maxwell J.: J. A. M. A. 138:747, 1948.

Dicumarol

20. Schofield, F. W.: Canad. Vet. Rec., 3:74, 1922. J. Am. Vet. M. A. 64:553, 1924.
21. Roderick, L. M.: Am. J. Physiol., 96:413, 1931.
22. Campbell, H. A. and Link, K. P.: J. Biol. Chem., 138:21, 1941.
23. Stahmann, M. A., Huebner, C. F. and Link, K. P.: J. Biol. Chem., 138:513, 1941.
24. Weiner, Murray, Axelrod, Julius, Shapiro, Shepard and Brodie, Bernard B.: Federation Proc., 8:345, 1949.
25. Meyer, O. O. and Spooner, M.: Proc. Soc. Exper. Biol. & Med., 54:88, 1943.
26. Loomis, E. C. and Seegers, W. H.: Am. J. Physiol., 148:563, 1947.
27. Munro, M. P. and Munro, F. L.: Am. J. Physiol., 150:409, 1947.
28. MacMillan, Robert L.: Science, 108:416, 1948.
29. Spooner, Maryloo and Meyer, Ovid O.: Am. J. Physiol., 142:279, 1944.
30. Rose, C. L., Harris, P. N. and Chen, K. K.: Proc. Soc. Exper. Biol. & Med., 50:228, 1942.
31. Wakim, K. G., Chen, K. K. and Gatch, W. D.: Surg. Gynec. & Obst., 76:323, 1943.

TREATMENT AND PREVENTION OF PULMONARY EMBOLISM, VENOUS THROMBOSIS AND OTHER THROMBO-EMBOLIC EPISODES

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The value of anticoagulants in the prevention and treatment of vascular thrombosis and embolism has been well established. If there were a single inexpensive laboratory determination that would allow us to predict the danger of thrombosis in an individual patient, the problem would be simple. Until such a determination is available, we can only give prophylactic anticoagulants to those patients whose disease increases their chances of a thrombo-embolic complication.

In an autopsy study of 370 cases of pulmonary embolism, Hampton and Castleman[1] found 60 per cent occurring in medical cases, 30 per cent of the total in patients with heart disease. In a study of 2613 autopsies, Burke[2] found 648 (24 per cent) to have thrombosis. Four hundred and twenty-seven of the thromboses occurred in strictly medical cases, of which 203 had various types of cardiac disease as the primary condition and 135 more as an important secondary condition. Hines,[3] in an au-

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topsy study of 234 cases of heart disease, found that gross pulmonary embolism occurred 81 times (35 per cent), yet a clinical diagnosis of pulmonary infarction was made only twice.

Because heart disease is such a prominent finding in most studies of thrombo-embolism, many physicians have advocated giving prophylactic anticoagulants to this group of patients when they become bedridden.

Nichol,[4] Peters *et al*,[5] Wright,[6-7] and others have made control studies of the administration of prophylactic dicumarol to cases of acute myocardial infarction with a significant reduction in the mortality and incidence of thrombo-embolism. Similar studies using cases of congestive failure have been undertaken.

Methods of preventing thrombo-embolism as advocated by our surgical colleagues are not applicable to most medical cases.

In the past two and one-half years, we have had the opportunity to administer anticoagulants to a number of patients in the Charity Hospital at New Orleans. The following is a summary of the study.

CONGESTIVE FAILURE

We set out to study two groups of patients, employing dicumarol in those of one group in addition to the usual methods of therapy, and using those of the other group as controls. During the study there developed, however, a third group of considerable size, made up of patients in whom the prothrombin activity was initially reduced to 50 per cent (or less) of normal, and who were, therefore, not given dicumarol.

Occurrence of Thrombo-Embolism. In the treated group of 147 cases of congestive failure, there were 11 deaths (7.4 per cent mortality) with 3 autopsies which did not reveal the presence of thrombi or emboli. There were only 2 cases that were suggestive of a thrombo-embolic complication.

Of the 38 "low" cases, there were 6 deaths (15.8 per cent mortality); 2 were autopsied and 1 found to have a pulmonary embolus.

In the control group of 150 cases of congestive failure, there were 20 deaths (13.3 per cent mortality); 8 were autopsied, 7 (35 per cent) having serious emboli. An additional 6 of the fatal cases were suspected of having a thrombo-embolic complication, but no autopsy was permitted. If the definite and suspected cases are combined, thrombo-embolism may have played a part in 65 per cent of the fatal cases in the control group (Table 1).

TABLE I

OCCURRENCE OF THROMBO-EMBOLISM IN 150 CONTROL CASES OF CONGESTIVE FAILURE

A. Fatal Cases	
I. Autopsy Diagnosis	
1) Pulmonary emboli with infarction	4
2) Multiple cerebral emboli with infarction	1
3) Mesenteric thrombosis with infarction	1
4) Bilateral auricular thrombi	1
	7
II. Clinical Diagnosis (not autopsied)	
1) Pulmonary infarction	1
2) Expired suddenly	5
	6
B. Non-Fatal Cases	
1) Pulmonary embolism (2 treated)	3
2) Thrombophlebitis	1
	4

11.3 per cent incidence of thrombo-embolism in 150 cases of congestive failure.

The total incidence of definite and suspected thrombo-embolism occurring in the 150 control cases of congestive failure was 11.3 per cent, as compared to 1 per cent in the 147 cases of congestive failure given prophylactic dicumarol.

MYOCARDIAL INFARCTION

Our series consists of 58 cases treated with anticoagulants and 144 controls obtained by a five year review of the Charity Hospital records. Only those cases that had unequivocal electrocardiographic evidence of a fresh myocardial infarction accompanied by a compatible history were included in the study. Those patients who were in the hospital less than three days were excluded. All electrocardiographic interpretations were made by members of the Charity Hospital Heart Station.

Results. There were 12 deaths (20.6 per

cent mortality) in the 58 anticoagulant treated cases, and 38 deaths (26.3 per cent mortality) in the 144 control cases.

Six (50 per cent) of the 12 fatal treated cases were autopsied and only 1 case was found to have a thrombo-embolic complication. This patient had luetic aortitis with subacute bacterial endocarditis (undiagnosed antemortem) in addition to a myocardial infarct. There was a ball valve thrombus attached to the aortic valve which caused intermittent closure of the mouth of the left coronary artery. This thrombus was undoubtedly present before treatment, as it gave rise to the myocardial infarction.

Fourteen (37 per cent) of the 38 fatal cases of the control group were autopsied and definite thrombo-embolism occurred in 8 (7 pulmonary emboli and 1 mesenteric infarction). Thrombo-embolism occurred in 4 cases not autopsied, 2 experiencing a cerebral embolus and 2 a pulmonary embolus.

Forty-six treated cases survived and experienced no suspected thrombo-embolic episode. One hundred and six of the control group survived, one experiencing a femoral artery embolus and the other thrombophlebitis of the leg.

The total incidence of thrombo-embolism in the 144 control cases of fresh myocardial infarction was 9 per cent.

In 38 deaths of the control group there were 14 autopsies (37 per cent). Definite thrombo-embolism occurred in 12 (31 per cent) of the fatal cases in the control group.

THROMBOPHLEBITIS

This series is comprised of 57 cases. Twenty were complications of a medical condition, 18 entering the hospital because of congestive heart failure. Twenty-five followed surgical procedures, and 12 had no obvious etiologic cause.

Fourteen patients experienced a pulmonary embolus before anticoagulants were started. Four patients had bilateral superficial femoral vein ligation before anticoagulants were started.

Results. One patient continued to have pulmonary emboli though he received a bilateral superficial femoral vein ligation and anticoagulants. Autopsy revealed widespread metastatic carcinoma of the pancreas. Anticoagulant failure has been previously noted in carcinoma of the pancreas.

Two patients had pulmonary emboli on the second and sixth days, respectively, of anticoagulant therapy; both survived.

One patient had a recurrence of thrombophlebitis and pulmonary embolism on the eleventh day after discharge. He had remained in bed at home. It is well known that anticoagulants should be continued until the patient is fully ambulatory.

In 33 cases there was no major illness which prevented the patient from becoming ambulatory as soon as the leg edema, temperature and pulse rate subsided. In these 33 cases the average day of ambulation was 8.5 days.

Residual. In most cases our follow-up was within the first month after discharge. Three required ace bandage. One had moderate swelling and 9 had slight swelling.

In 57 cases of thrombophlebitis treated with anticoagulants, 4 experienced further thrombo-embolic complications (7 per cent). There were 3 deaths, 2 from uremia and 1 from metastatic carcinoma of the pancreas complicated by thrombo-embolism.

PULMONARY EMBOLISM

In the last eighteen months we have treated 46 cases of pulmonary embolism. Fifty-four per cent occurred in strictly medical cases, and 46 per cent in surgical cases. Thirty-six cases were considered as definitely having experienced a pulmonary embolus, 5 probably, and 5 possibly. Twenty of the 25 medical cases had congestive heart failure upon admission; the remaining 5 had thrombophlebitis.

Eleven cases received emergency therapy of atropine and papaverine in addition to anticoagulants. All cases except 9 received heparin in addition to dicumarol until the prothrombin activity was reduced to the therapeutic range.

Further embolization after anticoagulant therapy occurred in five patients (10.8 per cent) at two hours; four hours; thirty hours (probable); sixth hospital day; and the fifth case expired (metastatic carcinoma of the pancreas).

There were 3 deaths in the definite group and 1 in the possible group, giving a mortality of 8.7 per cent.

Fifty per cent of the patients became ambulatory in ten days or less. The longest stay in bed was twenty-four days.

Those who survived and were discharged had no further thrombo-embolic complications except 1 patient who remained in bed at home eleven days and experienced another pulmonary embolus.

PELVIC THROMBOPHLEBITIS

This group is comprised of 6 cases. The first 3 cases treated had serious multiple pulmonary emboli and were too ill to have a vena cava ligation. The good results obtained with these three resulted in the Gynecology Service giving us 3 additional patients who were not critically ill. All 6 recovered with no sequelae.

ARTERIAL EMBOLI

This group is comprised of 3 cases who had one cerebral and two femoral emboli, respectively. All 3 had auricular fibrillation. After anticoagulants were given the mechanism was returned to normal with quinidine.

SUMMARY

1. In a control group of 150 cases of congestive heart failure the mortality was 13.3 per cent as compared to 7.4 per cent in 147 cases given prophylactic dicumarol.

2. Thirty-five per cent of the fatal cases in the control group of congestive failure definitely had a thrombo-embolic complication as proven by autopsy.

3. There was an 11.3 per cent incidence of thrombo-embolism in 150 control cases of congestive failure.

4. There were 2 cases of suspected thrombo-embolism in 147 cases of congestive failure treated with dicumarol.

5. In a control group of 144 cases of fresh myocardial infarction, the mortality was 26.3 per cent as compared to 20.6 per cent in 58 cases given prophylactic anticoagulants.

6. Thirty-one percent of the fatal cases in the control group of myocardial infarction definitely had a thrombo-embolic complication as proved by autopsy.

7. There was a 9 per cent incidence of thrombo-embolism in 144 control cases of myocardial infarction.

8. There was 1 case of probable thrombosis in the 58 cases of myocardial infarction given prophylactic anticoagulants.

9. The results in the treatment of thrombophlebitis with anticoagulants have been excellent.

10. In 46 cases of pulmonary embolism treated with anticoagulants the mortality was 8.7 per cent.

CONCLUSIONS

Our experience with the use of anticoagulants in a large number of cases confirms the experience of others in that heparin and dicumarol are effective in the prevention of vascular thrombosis and in the prevention and treatment of arterial and pulmonary embolism. In congestive heart failure the use of dicumarol prevented thrombo-embolic complications except in 2 possible cases, and effected a reduction in mortality which is probably significant and which can be attributed entirely to the prevention of thrombo-embolic complications. In our series of myocardial infarction there was no evident lowering of mortality from the use of anticoagulants, but in this connection it should be noted that our control series did not consist of parallel cases and it should also be noted that in the cases treated with heparin and dicumarol no thrombo-embolic complications were observed. Our results in the treatment of thrombosis of the leg veins have been good. Our statistics indicate a considerable lowering of mortality in cases of pulmonary embolism, there being only 4 deaths in a series of 46 cases. Six patients with septic phlebitis of the pelvic veins and 3 cases of arterial embolism were treated without mortality.

REFERENCES

1. Hampton, A. O., and Castleman, B: Correlation of postmortem chest teleoroentgenograms and autopsy findings with special reference to pulmonary embolism and infarction. Am. J. Roentgenol. 43.305, (March) 1940.

2. Burke, M.: Thrombosis: A medical problem. Am. J. Med. Sci. 196:796, 1938.

3. Hines, L. E., and Hunt, J. I.: Pulmonary infarction in heart disease. Ann. Int. Med. 15:644, 1941.

4. Nichol E. S., Page, Samuel W., Jr.: Dicumarol therapy in acute coronary thrombosis; results in 50 attacks J. Florida M. A. 32:365, (Jan.) 1946.

5. Peters, H. R., Guyther, R. J., and Brambel, C. E. Dicumarol in acute coronary thrombosis. J. A. M. A. 130:398, (Feb. 16,) 1946.

6. Wright, I. S.: Experiences with dicumarol (3,3 methylene-bis-4-hydroxycoumarin) in the treatment of coronary thrombosis with myocardial infarction. Am Heart J. 32:20, (July) 1946.

7. Wright, I. S.: The use of the anticoagulants in the treatment of diseases of the heart and blood vessels. Ann. Int. Med. 30:80, (Jan.) 1949.

SYMPOSIUM ON RICKETTSIAL DISEASES
CLINICAL ASPECTS OF RICKETTSIALPOX, Q. FEVER AND ROCKY MOUNTAIN SPOTTED FEVER*

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It is obviously impossible to cover all of the clinical features of rickettsial infection in a brief presentation. This discussion, therefore, will be confined to certain aspects of rickettsial disease which constitute recent advances in our knowledge of this complicated field, and which may be of present or future importance to physicians in this geographical area. Under such an elastic heading we will consider two rickettsial infections which are relatively new diseases, Rickettsialpox and Q. fever, and one older and more malignant ailment, Rocky Mountain spotted fever, which has steadily increased in importance in this country during the past decade and is now a more urgent problem for prompt diagnosis because of the availability of curative methods of treatment.

RICKETTSIALPOX

During the month of June 1946, an explosive epidemic of an unidentified disease swept through a housing development occupied by several hundred families in an isolated part of Queens County in New York City. The physician whose general practice included many of the families living in this area promptly recognized that he had something new on his hands, and an investigation which involved the joint efforts of the U. S. Public Health Service and the City Health Department was soon under way. Out of this investigation came, within a surprisingly short time, an almost complete picture of the clinical features, etiology, and mode of transmission of a brand new rickettsial disease.[1-2] In all, 144 cases were reported from the single housing development, and within the next few weeks about 50 other cases were detected in other parts of New York City. Moreover, shortly after the disease became publicized in the city, numerous physicians in other counties realized that they had been seeing within recent years sporadic cases of a precisely similar clinical syndrome. It is quite likely that the disease has existed in an unrecognized form for some time. There is no reason to assume that it will remain confined to the New York area for long, and indeed we may already have had it in this region without realizing it. Hence, a familiarity with the pertinent clinical features of rickettsialpox should be of value.

The disease began—although the patients were not yet aware that they were ill—with a single skin lesion which has been referred to as the "initial lesion". Most of the patients thought that they had developed a small boil; in some it was no more noticeable than a pimple. This lesion usually appeared on one of the covered parts of the body, and represented in all probability the site of original infection by the mite responsible for transmitting the disease. It started as a small, round, firm, dark red papule which grew in size, became vesiculated in the center, and then formed a dry black eschar. The skin surrounding the initial lesion was sometimes reddened but not indurated. Usually the regional lymph nodes were enlarged and moderately tender. The lesion usually lasted three or four weeks, sometimes considerably longer than the disease itself.

Not all patients were aware of the existence of the primary lesion, but in the series reported by Greenberg *et al.*[3] a careful inspection of the body revealed a lesion in 95 per cent of cases.

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About one week after the appearance of the initial lesion, the disease itself began. Like most rickettsial infections, the onset was very sudden and was characterized by chills, fever, weakness, and pain in the back. A temperature of 103° or 104° F. was common at the outset. In most cases the fever persisted, with morning remissions, for about a week, after which it gradually returned to normal. Chills were observed to occur during the first two or three days, sometimes with two or three chills each day. Headache was a prominent symptom in 90 per cent of the cases. Other symptoms included diffuse muscle pains, lassitude, photophobia, and in a few patients, persistent nausea and vomiting.

Sometime during the second, third, or fourth day after the onset of these symptoms, the rash made its appearance. In some individuals, the rash was noted at the same time as the first symptoms.

The characteristic rash of rickettsialpox consisted of discrete, red, maculopapular lesions which were firm to the touch. The base of each lesion was usually circular, and measured between 2 and 8 millimeters in diameter. These lesions appeared on the trunk, face, and extremities, and the pattern of their distribution varied considerably from patient to patient. Lesions were not noted on the palms or soles. In two patients lesions occurred on the palate and tongue.

Within twenty-four to forty-eight hours after the appearance of the papules, the lesions formed small vesicles at their summits; these vesicles were firm and were described as having the appearance of a "window" in the top of the papule. After several days the vesicles dried with a black crust, which was later discharged without leaving a scar.

In a few cases the spleen was palpable. Generalized lymphadenopathy was not observed.

All of the patients recovered without sequelae, and in most instances recovery was complete by the seventh to tenth day. Except for a mild leucopenia there were no significant laboratory abnormalities. Diagnosis was accomplished by the isolation of the causative agent from the blood, and by the demonstration of a specific complement-fixing antibody during convalescence.

In summary, rickettsialpox is an acute febrile disease which is characterized by an initial single pustular lesion of the skin, followed by a generalized eruption which is at first maculopapular and later becomes vesicular. It is obvious that if such an illness were observed in its sporadic form, it might be mistaken for chicken pox, and indeed, this happened in some of the early cases in the New York outbreak. However, the vesicle of varicella is elevated, superficial, and easily ruptured, while in rickettsialpox it is partially submerged within the papule. The presence of this disease in the United States should lead to a painstaking examination of all cases of "atypical" chicken pox, especially in adults and when the appearance of the rash is preceded by a sudden onset of fever a day or so earlier. Under such circumstances, the initial pocklike lesion should be sought for with care. In any case in which the diagnosis is suspected, special laboratory procedures should be undertaken which are similar to those used for the diagnosis of other types of rickettsial disease.

It is unlikely that this disease will often be confused with smallpox, in view of the relative mildness of rickettsialpox and the failure to develop a frankly pustular rash with the geographic pattern of smallpox. The vesicular character of the rickettsialpox lesion enables its differentiation from all other types of known rickettsial disease, including epidemic and endemic typhus, Rocky Mountain spotted fever, scrub typhus, and the Mediterranean disease known as Boutonneuse fever.

Concerning treatment of rickettsialpox little can be said at the present time. The organism is susceptible to both aureomycin and chloromycetin, and in the event of a new outbreak one of these substances would be indicated.

Q. FEVER

The second rickettsial infection which is still new to many of us, and which bids fair

to become of increasing importance in our population, is Q. fever. This disease differs from all other known rickettsial infections in its failure to produce skin lesions of any sort and in its particular predilection for the lungs. The disease which it most closely resembles and with which we are most apt to confuse it is primary atypical (or "virus") pneumonia.

Q. fever was first recognized in Queensland, Australia, in 1935[4], and a short time later a similar agent was isolated from naturally infected ticks in this country.[5] Except for frequent and sometimes spectacular infections among laboratory workers—entire institutes have contracted the disease—the illness appeared to be of no great significance until 1944 and 1945, when more than 1,000 cases suddenly occurred among Allied troops in the Mediterranean theatre.[6] Subsequently, new cases have occurred in this country among returned military personnel, and also among civilians, and the disease may be presumed to have gotten a firm foothold in some parts of America. In March 1946, an outbreak of Q. fever occurred among stock handlers and slaughterhouse workers in Amarillo, Texas.[7] At the present time, Q. fever is generally regarded as a potential epidemic disease of major importance, and there is every reason to believe that we will be seeing some of it here in Louisiana.

The disease begins, typically, after an incubation period of between two and three weeks, with an abrupt onset of headache, fever, and generalized body pains. The headache is severe and intractable and is often the complaint which brings the patient to his physician. During the first few days these are the only complaints, and the temperature ranges between 101° and 104° F. The pulmonary involvement which characterizes the later stage of Q. fever is not recognizable at this time; there is no cough, and the lungs appear normal by x-ray. After three or four days the x-ray shows patchy areas of consolidation in a portion of one lobe, generally with a ground glass appearance. At about the same time, scattered crepitant rales may be heard over the involved area, perhaps with slightly impaired resonance. The patient develops a mild cough, usually unproductive, and may complain of vague pains in the chest on the affected side. A few patients become slightly cyanotic, but the dyspnea and respiratory distress of bacterial pneumonia are unusual in this disease. The pulse rate is not as rapid as would be expected with the amount of fever. The white cell count and blood smear are within normal limits.

The illness persists for seven to ten days and usually subsides without complications or sequelae. A few instances of pleurisy and effusion have been described, and arthritis and orchitis have occurred as late complications.

Obviously, such a disease would be difficult to distinguish from primary atypical pneumonia, either by clinical judgment or x-ray study. The differentiation is a laboratory problem, and hinges on the specific serological tests for the identification of Q. fever which will be described in another paper.

Since most cases recover quite readily from Q. fever, specific therapy is not a major problem. In severe infections, either chloromycetin or aureomycin should be effective.

ROCKY MOUNTAIN SPOTTED FEVER

In 1899, Maxey,[8] writing in the "Medical Sentinel", of Portland, Oregon, described the disease which we call Rocky Mountain spotted fever as follows: "An acute, endemic, non-contagious but probably infectious, febrile disease, characterized clinically by a continuous moderately high fever, severe arthritic and muscular pains, and a profuse petechial or purpural eruption in the skin, appearing first on the ankles, wrists, and forehead, but rapidly spreading to all parts of the body." No better nor briefer description of the disease has since been written. During the next several decades it was learned that the fever was caused by a species of rickettsia (*Dermocentroxenus rickettsi*) and transmitted to man by the bite of an infected tick. The disease has occurred in almost all parts of the country, including forty-three states.

Until very recently it has been one of the most formidable of deadly diseases, with devastating effects on body tissues and a high mortality. It did not respond to treatment with the sulfonamides, penicillin, or streptomycin. Indeed, there is some evidence that sulfonamides actually have an adverse effect in this disease. Owing to the extraordinary generalized vascular injury which characterizes the disease, the patients often perished in a form of medical shock against which large amounts of plasma and blood transfusion were only partly effective. Harrell and his co-workers[9] demonstrated that there occurs a widespread loss of circulating fluid into the tissues, which is attended by a marked fall in blood chloride and an elevation of the NPN to uremic levels. Valiant attempts to combat this disturbance of fluid equilibrium were made in many patients, but the mortality continued to range around 25 per cent or higher. The use of specific antiserum was advocated by Topping,[10] but this was of questionable value after the full development of the disease.

The first promise of specific chemotherapy was offered in 1942, when Snyder and his co-workers[11] showed that paraaminobenzoic acid possessed rickettsiastatic properties. Clinical trials of this drug demonstrated its partial effectiveness in lowering the mortality in Rocky Mountain spotted fever but left much still to be desired by the clinician. It was most effective when given in very large doses, such that blood levels of 50 to 70 milligrams per cent were obtained.

Recently two new antibiotic agents have become available for the treatment of rickettsial disease, and both have been shown to be highly effective against Rocky Mountain spotted fever. These are aureomycin[12] and chloromycetin,[13] either of which is capable of bringing about the subsidence of fever and relief of symptoms within two to three days after administration. Both drugs are given by mouth, and both seem thus far to be almost without toxic reactions other than occasional nausea and vomiting. There is not yet enough evidence in the literature to allow one compound to be favored above the other in rickettsial infection, and more extensive clinical trials are needed. There is at this time no doubt, however, that either substance is a nearly ideal therapeutic agent in rickettsial disease, and notably so in Rocky Mountain spotted fever. The optimal doses have not yet been firmly established for either drug. Successful treatment has been reported with an initial dose of 60 milligrams per kilogram of body weight, followed by 0.25 grams every three hours until the temperature remains normal for forty-eight hours.

REFERENCES

1. Shankman, B.: Report on an outbreak of endemic febrile illness, not yet identified, occurring in New York City. New York State J. Med., 46:2156, 1946.

2. Huebner, R. J., Stamps, P., and Armstrong, C.: Rickettsialpox—a newly recognized rickettsial disease. I. Isolation of the etiological agent. Pub. Health Rep., 61:1605, 1946.

3. Greenberg, M., Pellitteri, O., Klein, I. F., and Huebner, R. J.: Rickettsialpox—a newly recognized rickettsial disease. II. Clinical observations. J. A. M. A., 133:901, 1947.

4. Derrick, E. H.: "Q" fever, a new fever entity: clinical features, diagnosis and laboratory investigation. M. J. Australia, 2:281, 1937.

5. Davis, G. E., and Cox, H. R.: A filter-passing infectious agent isolated from ticks. I. Isolation from *Dermacentor andersoni*, reactions in animals, and filtration experiments. Pub. Health Rep., 53:2259, 1938.

6. Robbins, F. C., Gauld, R. L., and Warner, F. B.: Q Fever in the Mediterranean area: report of its occurrence in Allied troops. II. Epidemiology. Am. J. Hyg., 44:23, 1946.

7. Topping, N. H., Shepard, C. C., and Irons, J. V.: Q fever in the United States. I. Epidemiologic studies of an outbreak among stock handlers and slaughterhouse workers. J. A. M. A., 133:813, 1947.

8. Maxey, E. E.: Some observations on the so-called spotted fever of Idaho. Med. Sentinel, Portland, Oregon, 7:433, 1899.

9. Harrell, G. T., Venning, W., and Wolff, W. A.: The treatment of Rocky Mountain spotted fever, with particular reference to intravenous fluids. A new approach to basic supportive therapy. J. A. M. A., 126:929, 1944.

10. Topping, N. H.: Rocky Mountain spotted fever. Further experience in the therapeutic use of immune rabbit serum. Pub. Health Rep., 58:757, 1943.

11. Snyder, J. C., Maier, J., and Anderson, C. R.: Report to the Division of Medical Sciences, National Research Council (Dec. 26), 1942.

12. Wong, S. C., and Cox, H. R.: Action of aureomycin against experimental rickettsial and viral infections. To be published.

13. Pincoffs, M. C., Guy, E. G., Lister, L. M., Woodward, T. E., and Smadel, J. E.: The treatment of Rocky Mountain spotted fever with chloromycetin. Ann. Int. Med., 29:656, 1948.

THE LABORATORY DIAGNOSIS OF RICKETTSIAL DISEASE*

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NEW ORLEANS

Rickettsiae are obligate intracellular parasites, that is, they require living cells for their proliferation. This fact is basic to a consideration of the laboratory precedures designed for the confirmation of the clinical diagnosis of the several human diseases caused by these agents. Based on the distinct etiological agent responsible for each of the several types of these diseases and their antigenic relation to one another the following classification will prove most useful for the purpose of this discussion.

TABLE I

1. Typhus Group.
   a. Epidemic typhus (*R. prowazeki*)
   b. Murine typhus (*R. mooseri*)
2. Spotted Fever Group.
   a. Rocky Mountian spotted fever (*R. rickettsi*)
   b. Boutonneuse fever (*R. conori*)
   c. Rickettsial pox (*R. akari*)
3. Tsutsugamushi disease or scrub typhus (*R. orientalis*)
4. Q. fever (*R. burneti*)

In the geographic area with which we are immediately concerned murine typhus and Rocky Mountain spotted fever are well recognized. The more recently identified and characterized Q. fever and rickettsial pox should be of considerable concern as the possibility of their occurrence is more than likely in this region. Epidemic typhus may be considered as a more remote possibility and neither boutonneuse fever or scrub typhus are of immediate concern.

The most important factor in the proper diagnosis of murine typhus and Rocky Mountain spotted fever is the early clinical recognition of these diseases. If and when scrub typhus or rickettsial pox is encountered, the fact that clinicians are aware of the possibility of their occurrence and cognizant of their clinical features will undoubtedly be the first step toward their proper identification.

Early clinical diagnosis is all the more essential in view of the proved efficacy of the more recent therapeutic advances, especially with the development of the antibiotics chloromycetin and aureomycin which have proved effective in these infections. Early treatment is essential and must be instituted before the laboratory can produce the answer which confirms the clinical diagnosis.

It is, therefore, all the more important that the physician understands and properly carries out those procedures upon which successful laboratory results depend. Two main types of procedures for the diagnosis of rickettsial diseases are available: (1) The isolation and identification of the etiological agent and, (2) serological methods.

ISOLATION AND IDENTIFICATION OF THE RICKETTSIAE

These methods can be performed only where adequate laboratory facilities and considerable experience with these methods are available. The rickettsiae of murine typhus and of Rocky Mountain spotted fever are present in the blood of patients during the early stages, especially the first four to six days of the disease. Inoculation of 3 to 5 c.c. of citrated blood, or more preferably, directly from the syringe with which it is withdrawn from the patients, into male guinea pigs will in about 60 to 75 per cent of instances produce a characteristic febrile disease and a typical scrotal reaction. Clotted blood which is first macerated before inoculation has also been used successfully. The following chart illustrates the type of disease produced and the characteristics which serve to differentiate epidemic typhus, murine typhus and Rocky Mountain spotted fever.

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TABLE II

Differential Characteristics of the Disease Produced in Guinea Pigs Inoculated with Blood from Early Febrile Patients with Rickettsial Infections.

Characteristics	Epidemic Typhus	Murine Typhus	R.M.S. Fever
Scrotal Swelling	none	present without necrosis	present with necrosis
Fever	10-16th day	4th to 8th day (usually moderate)	3rd to 14th day (usually high)
Identification of Rickettsia.	Inoculation of G. P. brain into yolk sac of chick embryo.	Demonstrated in direct stained smear of tunica.	Inoculation of spleen or blood of G. P. into yolk sac or tissue culture.

Q. fever rickettsiae can be isolated by inoculating guinea pigs with blood or urine from patients in the early febrile period. The rickettsiae of rickettsial pox can be isolated in white mice by inoculation of whole blood.

The most generally useful methods for the laboratory diagnosis of rickettsial diseases are serological procedures designed to demonstrate the appearance of specific antibodies in the patient's blood and their increase in titer during the course of infection and convalescence. The best assistance to the clinician can be given if at least three blood samples are submitted to the laboratory, (1) during the first few days of illness, (2) during the second week, and (3) toward the end of the third week. It is of the utmost importance that the laboratory be informed of the period of the disease at which the blood was drawn. One sample of blood is not adequate for proper diagnosis. Several serological tests are available of which at least two should be run by a well equipped laboratory.

Although the Weil-Felix test is a non-specific reaction it is, nevertheless, frequently used and is sufficiently useful for the early presumptive diagnosis of several rickettsial diseases to warrant continued consideration. In the following table the usual Weil-Felix reactions observed are represented.

	OX19	OX2	OX-K
Epidemic typhus	+ + + +	+	—
Murine typhus	+ + + +	+	—
Scrub typhus	—	—	+ + + +
Q. fever	—	—	—
Rocky Mt. sp. fever	+ + + +	+	—
		or	
		+	+ + + +

The agglutininins for the Weil-Felix intigens are frequently present as early as the sixth day of the disease and practically always by the twelfth day. As such they often provide the first presumptive labora-

TABLE III

The Specific "In Vitro" Serological Tests in Murine Typhus, R.M.S. Fever, Q. Fever and Rickettsial Pox

Type of Disease	Complement Fixation				Agglutination			
	Rickettsial Antigen				Rickettsial Antigen			
	Mur. T	R.M.S.	Q. Fever	R.P.	Mur. T.	R.M.S.	Q. Fever	R. P.
Murine Typhus	+	+*	—	—	+	+*	—	—
R. M. S.	+	+*	—	—	+	+*	—	—
Q. Fever	—	—	+	—	—	+	—	—
Rickettsial Pox	—	—	—	+	Not used.			

*Cross reactions can be eliminated by using rickettsial suspensions repeatedly washed to remove the soluble antigens.

*Considerable cross reactions occur when formalin killed antigen suspension is used.

tory indication of the nature of the disease in question. A positive test on a single blood specimen should not be relied upon unless the test is high, 1-320 or over. The antibodies to the Weil-Felix antigen do not tend to persist longer than several months after convalescence.

The specific serological tests for rickettsial infections depend on the use of antigen suspensions of the distinct types of rickettsial responsible for each form of the disease. These were not available for general use until the yolk sac of the developing chick embryo was found to be suitable for their propagation. The complement fixation test is most generally used and available in most laboratories. Agglutination and precipitin tests are available but not in general use, except for special instances where exact differentiation is required. The preceding table represents the application of the specific serological tests.

The complement fixing antibodies to the rickettsial infections usually appear during the second week of illness. Unlike the antibodies to the Weil-Felix antigen which disappear rather rapidly, these antibodies persist for at least six to eight years. This test, therefore, is useful not only for purposes of diagnosing current infections but is of great value for epidemiological studies.

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PATHOLOGY OF RICKETTSIAL DISEASES IN MAN*

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NEW ORLEANS

There are several human infections induced by microorganisms called rickettsiae. These organisms are intermediate in their characteristics between bacteria and viruses. They are readily seen under the microscope as pleomorphic cocco-bacillary forms. They multiply only within certain cells of susceptible species and are found in various arthropods in nature. On the basis of clinical features, epidemiologic aspects, serologic and immunologic characteristics, these rickettsial diseases of man are divided into the following five groups.[1]

1. Typhus group
   a. Classic epidemic (louse-borne) typhus, *R. prowazeki prowazeki*
   b. Murine (flea-borne) typhus, *R. prowazeki mooseri*
2. Spotted fever group (tick-borne) *R. rickettsi*
3. Scrub typhus (Tsutsugamushi disease) (mite-borne) *R. orientalis*
4. Q. fever (tick-borne) *R. burneti (diaporica)*
5. Trench fever (lice) *R. pediculi* (?)

Most of our discussion will concern itself with typhus fever, Rocky Mountain spotted fever, and scrub typhus. The tick-borne, the louse-borne and the mite-borne rickettsial diseases have as their distinctive pathology lesions of the small blood vessels chiefly of the skin and subcutaneous tissues and of the central nervous system. Since the lesions involve for the most part blood vessels microscopic in size, gross lesions are not prominent. The organisms gain entrance to the blood stream and are carried in small numbers to the capillary bed in all parts of the body where they may undergo extensive multiplication particularly in the endothelial cells lining capillaries of the brain, skin and heart.[2] It is the lesion found in the capillaries and the blood vessels of the precapillary size in the skin which produce the eruption noted in these diseases. The rickettsiae are demonstrated fairly easily in sections in Rocky Mountain spotted fever and less easily is epidemic typhus. For this reason one may say that localization of rickettsiae determines the site of the lesion. However, it has been suggested by some authors that indirect, possibly toxic, but more likely hyperergic effects of the rickettsiae, may be important in the pathogenesis of rickettsial pathology particularly in scrub typhus.[3] In scrub typhus, although no adequate attempts have

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been made to determine the rickettsiae, the analogies apparent after study of the disease suggest that in mite-borne disease the vascular lesions also follow the localization of the parasite.[4]

The skin and subcutaneous tissues are best for the study of vascular lesions which, throughout the body, are least severe in scrub typhus and most severe in Rocky Mountain spotted fever. In typhus the pathology varies from early swelling of the endothelium of capillaries, arterioles, and venules, to mural and occluding thrombi of fibrin, which occur first in the arteries and veins in the midzone of the corium, and later in the larger arteries and veins in the deepest zone of the corium and subcutaneous fat.[4] Necrosis of skin and subcutaneous tissues occurs in typhus usually only in regions subjected to pressure. In scrub typhus the blood vessel lesions progress but slightly beyond the initial stages of typhus; namely, occlusion of capillaries with perivascular mononuclear cell infiltration. In Rocky Mountain spotted fever necrosis of the media of arteries and veins of the skin and subcutaneous tissues takes place because of invasion of smooth muscle cells by rickettsiae and is independent of stasis produced by pressure. These vessels may have associated thrombosis. This then is reflected in the more hemorrhagic appearance of the rash and more frequent skin necrosis, particularly of the scrotum, fingers, toes, elbows, and ears. The local site of inoculation shows necrosis in scrub typhus. This is considered to be caused by the combined action of the secretion of the larval mite and the inoculated rickettsiae. The vascular lesions and perivascular infiltrations which are present in the surrounding viable tissue are similar to the reaction described elsewhere.

In the above three diseases the changes in the blood vessels within the viscera correspond in severity with those of the skin and subcutaneous tissues. It has been noted that vascular lesions may be found in any tissue or organ and the importance of such lesions varies with their number and the function of the organ in which the lesions occur.[4]

There is a great deal of interest in the pathologic changes found in the central nervous system. The histopathologic findings include infiltration in the leptomeninges, perivascular accumulation of cells, sharply circumscribed focal lesions or "nodules" of miliary and submiliary size, and slight cerebral edema. The meningeal infiltrations and perivascular accumulation of cells are the same in the three diseases, namely, mononuclear cells, lymphoid cells, and plasma cells. The extent of the pathologic changes in the leptomeninges is greatest in scrub typhus, and least in Rocky Mountain spotted fever.

The "nodules" have been found most frequently in typhus fever, and scrub typhus, and less consistently in Rocky Mountain spotted fever. They may be found in both grey and white matter in typhus fever and scrub typhus but are found most frequently in the grey matter.[5] In Rocky Mountain spotted fever somewhat larger vessels are more often involved and focal areas of demyelinization, and microinfarcts are produced.

The cellular composition of these "nodules" varies quantitatively and is influenced by the severity of the initial vascular lesion and by the time of the survival before death. The histologic components of these proliferative foci are predominently neuroglial cells with few lymphocytes and plasma cells. They are generaly considered to be in relation to a blood vessel, although the vessel may not be visible. Qualitatively the "nodules" of scrub typhus and Rocky Mountain spotted fever are similar.[4]

In the heart, the order of decreasing severity of involvement is scrub typhus, typhus, and Rocky Mountain spotted fever. Here we may see swelling of endothelial cells, histiocytes, plasma cells, lymphocytes, and occasional thromboses. These findings may be focal or diffuse.

In the lungs, the diffuse infiltration produces compression and blockage of alveolar capillaries as the cells accumulate inside as well as outside the capillaries. In scrub ty-

phus the reaction is most marked and is usually negligible in typhus. Branchopneumonia of bacterial origin is a common complication in fatal cases.

The kidneys in all three diseases show generalized blood vessel lesions and diffuse cellular infiltrations. We have therefore an interstitial nephritis and may have an early diffuse glomerulo-nephritis manifested by proliferation of endothelial cells with thickening of the basement membrane of glomerular capillaries. The glomerular changes are probably indirect effects either toxic or hyperergic. They are similar to lesions seen in many other infectious diseases.[3]

Lesions of the adrenal cortex are found in all three diseases such as blood vessel changes with associated focal areas of infiltration composed mainly of mononuclear cells. In addition, there are foci of lipid depletion, foci of lymphoid and plasma cell infiltration, and small areas of degeneration of the fascicular zone.

The liver reveals widespread swelling of the endothelium. Large mononuclear cells are usually present between the sinusoids and liver columns and within the periportal spaces. Individual and groups of liver cells may become necrotic and liver cell columns may be disrupted.

The spleen shows marked engorgement, lymphoid depletion of pulp, inactive follicles and a great increase of macrophages in the sinuses and reticular cords. Neutrophils appear late in the course of the disease and earlier if extensive pneumonia is present. In a small percentage of cases, focal areas of necrosis of the pulp may be present.

The lymph nodes in all three diseases undergo some form of hyperplasia with increase in macrophages. In scrub typhus necrosis of lymph nodes may be present.[5]

Q. fever is not accompanied by a rash. Clinically and pathologically it is different from the other rickettsial diseases. Owing to the low mortality, there have been few postmortem studies. In man no important lesions are found outside of the lungs. Pleural effusions are common. The pathologic changes in the lungs are those of a patchy interstitial pneumonia with considerable exudation. This exudate is composed of fibrin, lymphocytes, plasma cells, large mononuclear cells, and red blood cells. The alveolar walls are infiltrated with mononuclear cells. The respiratory bronchioles and alveolar ducts are also involved in the inflammatory process. One may see organization of the exudate in the alveoli in some areas while early infiltration and exudation may be seen in others.

Trench fever is not a fatal disease and therefore nothing is known about the lesions in the internal organs except that the spleen is enlarged to palpation. The cutaneous lesions show perivascular lymphocytic infiltrations and hyperplasia of the capillary endothelium but no specific changes are present.[4]

Rickettsial pox is a newly recognized disease characterized by an initial lesion caused by the bite of an infected mite. The organism recovered from the mite has been named *Rickettsia akari.* About one week prior to the onset of the fever, a red papule appears at the site of a mite bite and develops into a deep seated vesicle which ultimately shrinks and dries to form a black eschar. The regional lymph nodes usually become enlarged and are tender. A rash appears most commonly at the onset of fever or several days later. Since there have been no deaths, the pathologic picture in man is unknown except for the vascular and perivascular inflammatory changes in the skin. Mice inoculated intraperitoneally may show a small amount of blood tinged peritoneal fluid, enlarged lymph nodes, an enlarged edematous liver, and a dark, engorged spleen eight to ten times the normal size. The respiratory and intestinal tracts show no gross changes.[4]

In conclusion we may say that in general, in rickettsial diseases, the blood vessels are the tissues primarily involved. The first changes are proliferative in character due to actual invasion of cells by rickettsiae. Extravascular accumulations of mononuclear cells also occur about blood vessels in the skin and various other organs. All grossly visible effects are due to lesions of

blood vessels, as exemplified by the rash, the skin necroses and the neurologic manifestations.

REFERENCES

1. Snyder, John C.: Viral and Rickettsial Infections of Man, National Foundation for Infantile Paralysis, Inc., Lippincott, Co., Phila. Pa., 1948.
2. Anderson, W. A., Pathology, C. V. Mosby Co., St. Louis, 1948.
3. Allen, A. C., and Spitz, S.: Comparative study of pathology of scrub typhus (Tsutsugamushi disease) and other rickettsial diseases, Am. J. Path. 21:603, (July) 1945.
4. Rickettsial Diseases of Man, American Association for the Advancement of Science, Washington, D. C., 1948.
5. Ash, J. E., and Spitz, S.: Pathology of Tropical Diseases, W. B. Saunders, Philadelphia, Pa., 1945.

SOME EPIDEMIOLOGIC AND PUBLIC HEALTH ASPECTS OF TYPHUS AND ROCKY MOUNTAIN SPOTTED FEVERS*

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NEW ORLEANS

Since most of the members of this section will be concerned with medical problems as they exist in Louisiana. I will devote the time available to a discussion of the epidemiology and public health aspects of those rickettsial diseases which have been reported as occurring within the state. Brief mention will be made of other diseases in this group that have a related interest.

MURINE TYPHUS

Of the rickettsial infections, murine typhus has been reported in Louisiana more often than any other. This disease has been summarized as being a relatively mild, acute febrile illness of nine to fifteen days duration, characterized by headache and a macular rash. It is a natural infection of rats and mice transmitted sporadically to man by the rat flea, *X. cheopis*. The etiologic agent is *Rickettsia mooseri*.[1] During the period 1939-1948 there was a total of 2004 cases of murine typhus in Louisiana, this being one of the eight states (Alabama, Florida, Georgia, Louisiana, Mississippi, North Carolina, South Carolina and Texas) in which the major portion of typhus occurs in the United States.

As illustrated in chart I a steady increase in the cases of murine typhus reported occurred from 1939 to 1945 at which time 423 cases represented the peak occurrence. Following this period the incidence of this disease declined rather sharply until a low of 53 cases was reported in 1948. During the first four months of 1949 only 5 cases are known to have occurred. This progressive increase and subsequent decline in cases in Louisiana follows very closely the experience of the United States in general. Of the 2004 cases reported during the 1939-48 period, 76 resulted in death giving a case fatality rate of 3.8 per cent. This is somewhat higher than the average for the United States.

CHART I

REPORTED CASES AND DEATHS FROM MURINE TYPHUS IN LOUISIANA

1939-1948

Year	Cases	Deaths	Year	Cases	Deaths
1939	117	2	1944	283	11
1940	118	5	1945	423	14
1941	201	7	1946	287	8
1942	165	7	1947	125	8
1943	232	10	1948	53	4
Total Cases—2004			Total Deaths—76		

The distribution of murine typhus during 1939-48 has apparently been greatest in the southern portion of the state. Six parishes within the state did not report any cases. The greatest number of infections were concentrated in the following parishes: Orleans (596), Iberia (104), Calcasieu (118), Caddo (95), Washington (109), Avoyelles (72), Lafourche (64). During 1945 the peak incidence year, Orleans Parish reported 118 cases. The next largest number was reported from Iberia Parish (43), Caddo (38 cases), Calcasieu (26 cases), Washington (23 cases), Lafourche 18 cases), East Carroll (17 cases), Avoyelles (13 cases), Vermillion (11 cases). Except for Caddo and East Carroll parishes, the concentration of cases seemed to be greatest in the lower third of the state and here the predominance was apparently as-

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sociated with areas where the density of population was greatest or where environmental factors best favored a comparitively large rat population. Reports obtained from the Public Health Entomologist of the State Department of Health,[2] indicate that the rat flea, *X. cheopis*, which is the principal vector transmitting typhus from the rat reservoir to humans, is available over the entire state, but is found in greatest concentration in the lower portion. This finding is of interest in connection with the occurrence of the major number of human infections in the same area.

A study conducted by C. R. Eskey and F. M. Hemphill of the U. S. Public Health Service, Communicable Disease Center, Atlanta, Ga.[3] has yielded some interesting information concerning the occurrence of typhus in relation to the latitude and the related average temperature of the area involved. The accompanying table taken from their report shows that their studies in Louisiana during the six year period 1939-1944 reveal the annual average incidence of typhus to decrease progressively as the degree of north latitude increases.

CHART II

RELATION OF LATITUDE AND THE AVERAGE ANNUAL INCIDENCE OF MURINE TYPHUS PER 100,000 POPULATION IN LOUISIANA FOR THE PERIOD 1939-44

Degree North Latitude	Annual Incidence of typhus
33-32	3.2
32-31	5.1
31-30	8.3
30-29	9.2

(Extracted from article by Eskey and Hemphill, Public Health Reports, Vol. 63, No. 29, p. 941, July 1948)

On the basis of general information available, murine typhus has its peak incidence in the summer and early fall, usually during the months of July, August, and September. This infection is essentially a disease of the common rat which serves as the reservoir. Infection is transmitted from rat to rat by means of the rat flea, principally *X. cheopis* in this area. Also of importance in transmission of typhus from rat to rat is the rat louse. This latter vector is not of importance in transmitting the disease to man.

Human infection with murine typhus is usually considered to be an accidental transmission of the disease from rat to man by way of the rat flea. The flea becomes infected by feeding on the rat during an acute phase of the disease. When the flea population among rats becomes rather large many of the fleas desert the rat host and attack man. At the time of feeding the flea usually defecates and it is the infectious excreta that provides the transmission of rickettsia to the human host. There is no evidence that human infection has resulted from the bite of the flea. The irritation that follows the flea bite usually causes scratching resulting in the infectious excreta being rubbed into the abraded skin.

The influence of climate on the incidence of typhus mentioned previously is probably associated with a change in activity that occurs in the rat flea as a result of temperature variation. There is also the possibility that opportunity for exposure to infected fleas may have some relationship to the types of clothing worn at various periods of the year and also to the activity on the part of the human that brings him in closer contact with infectious areas.

An infection with murine typhus usually confers immunity to the individual which may last for many years. This infection also produces a certain degree of immunity against the epidemic type of typhus infection. Re-infection in the same individual may occur but this is not the rule.

The hazard from murine typhus has been associated with occupation and place of residence. It has been observed more often in persons employed around grain and feed mills and in food handlers who work in establishments that favor rat harborage or provide a feeding area for the rat population. Persons living in close proximity to garbage dumps or in rat infested dwellings are subject to increased hazard. Transmission of the disease from one human to another has not been observed. In most surveys a predominance of infected rats has been observed in the business districts of urban areas; however, studies in some por-

tions of the typhus area of the country indicate that there is sufficient infection of the rural rat population to make control measures of intensive nature justified in these areas.[4]

Infection with murine typhus has been shown to involve adult groups more often than young children. This is probably associated with the concentration of infected rats and their accompanying ecto parasites to the commercial areas of most cities where large numbers of children are not usually found. Opportunity for exposure is apparently the important factor.

Measures for the control of murine typhus should be directed against the reservoir of the disease, the rat, and the transmitting vector, the rat flea. The principal points in this program involve:

1. The elimination of garbage dumps and the correction of improper methods of garbage collection and disposal.

2. Elimination of rat harborage by rat proofing all new buildings and repairing old constructions in the proper manner.

3. Destruction of the rat reservoir by means of poisoning, trapping, or other effective means.

4. Control of the rat flea by the application of DDT dust to runways and harborages as a preliminary measure to trapping or poisoning. Where the elimination of the rat population cannot be accomplished completely the continued application of DDT dust (5-10 per cent dust) will produce a significant reduction in the flea population and will aid in controlling human infection.

5. A satisfactory vaccine against murine typhus has been prepared by the chick embryo method (Cox type vaccine). Use of the vaccine on a generalized basis is not recommended under ordinary conditions. Chief emphasis should be placed on control measured related to sanitation as mentioned above. The vaccine may be used to good advantage when an epidemic outbreak of typhus is anticipated, or as a routine measure for persons whose occupation requires them to be in close contact with the rat flea.

It should be borne in mind that the vaccine against murine typhus does not confer immunity against the epidemic typhus infection and vice versa.

EPIDEMIC TYPHUS

Epidemic typhus is a much more serious and severe infection than the murine form of the disease. The causative agent of this disease is designated as *Rickettsia prowazeki.* Man is the reservoir, and transmission occurs from person to person by means of the body louse. Evidence has also been presented that the inhalation of dried feces from infected lice may be a means in transmitting this infection.

Epidemic typhus usually occurs in connection with conditions associated with human misery, conditions created by war, famine, and other disastrous circumstances that produce crowded living conditions and improper personal hygiene. Major incidence is usually during the winter or early spring. The mortality rate may vary from 10 to 40 per cent. It is comparatively milder in children under age 15.

Control measures against epidemic typhus are directed principally to the elimination of the body louse. Use of DDT powder on the body and clothing have proved to be very effective. One adequate application of DDT will give protection against lice for several days, often as long as two weeks.

An effective vaccine against epidemic typhus has been developed. The "Cox type" vaccine prepared by chick embryo methods has been given widespread use. This material is a valuable adjunct in immunizing persons likely to be involved with epidemic typhus outbreaks. It was especially important in connection with protection of military personnel.

Epidemic typhus has not been a serious problem in the United States.

ROCKY MOUNTAIN SPOTTED FEVER

Rocky Mountain spotted fever is a rickettsial infection that will probably have an increasing interest for physicians in Louisiana. The etiologic agent for this disease is designated as *Rickettsia rickettsii* (*Dermacentroxinus rickettsii*). This disease was made reportable in Louisiana in 1943.

Information obtained from the Louisiana State Department of Health indicates a total of 17 cases recorded during the period 1942-48.

ROCKY MOUNTAIN SPOTTED FEVER REPORTED IN LA. 1942-1948

Year	Cases
1942	1
1943	2
1944	2
1945	1
1946	4
1947	3
1948	4

Parishes involved were: Caddo (3 cases), Webster (2 cases), Union (1 case), Winn (2 cases), La Salle, (1 case), Vernon (2 cases), Rapides (1 case), Ascension (1 case) and Tangipahoa (4 cases).

Originally this infection was considered to be restricted to the northwestern part of the United States in the region of the Bitter Root Valley of Montana. It has subsequently been reported in 41 states.

Several species of tick are capable of transmitting Rocky Mountain spotted fever, the principal variety being *Dermacentor andersonii* (wood tick) in the western part of the United States; *Dermacentor variablis* (American dog tick) in the eastern United States; and in the southern areas the varieties known as *Amblyomma americanum* (lone star tick) and sometimes the brown dog tick, *Rhipicephalus sanguineus.*

Surveys by the Public Health Entomologist of Louisiana show *Amblyomma americanum* to be abundant over the state. *D. variablis* is found more often in the northern portion of Louisiana and *Rhipicephalus sanguineus* is fairly prevalent during the early season of the year.

The tick is able to transmit the rickettsial infection to its progeny and thus serves as a reservoir of Rocky Mountain spotted fever. A large number of animals, both large and small, serve as hosts for *D. Andersonii*, furnishing a blood meal for the survival of the larvae, nymphs, or adults. The adult tick bites man readily.

Rocky Mountain spotted fever occurs chiefly during April and May in the western United States, this being the period of principal activity of the tick vector. In the eastern United States and southern areas the season may extend over a longer period of time.

Attempts to control the vectors of spotted fever have not proved very successful. Personal hygiene, protective clothing, avoidance of danger areas during the tick season and careful search for ticks to remove them before biting takes place have proved to be more efficacious.

Effective immunity against Rocky Mountain spotted fever may be obtained from vaccines that have been developed. The vaccines should be administered in spring or early summer before the tick season begins. This protection is particularly valuable to persons whose occupation, or sport habits take them into areas where infected ticks are likely to be found.

REFERENCES

1. Viral and Rickettsial Infections of Man, edited by Thos. M. Rivers, chapter 32, p. 483.

2. Personal communication from E. B. Johnson, Public Health Entomologist, La. State Board of Health.

3. Eskey, C. R., and Hemphill, F. M.: Relation of reported cases of typhus fever to location, temperature and precipitation. Pub. Health Rep., 63:941 (July 16) 1948.

4. Hill, Elmer L., Sr. and Ingraham, Samuel C., II: A study of murine typhus fever in Coffee County, Alabama. Pub. Health Rep., 62:875, (June 13) 1947.

DISCUSSION

Dr. B. E. Nelken: I wonder if the pathologists or bacteriologists could tell me why Q. fever which doesn't agglutinate the Proteus group and causes no rash, was placed in the Rickettsial group?

Dr. Buddingh: For the simple reason that the Rickettsiac are recoverable from that disease, and they have all the diagnostic characteristics of rickettsiae. The primary pathological reaction is just like you would see in the rickettsial disease, but the organism is definitely that of rickettsial disease.

Dr. G. Carrera: As regards Q. fever, I would like to pass a bit of information which might be interesting or important to pathologists. A few weeks ago, Dr. Dyer, the director of the National Institutes of Health, told us in a lecture at Tulane, that he knew of a patient who died eight or nine years after having had Q. fever, and the organism was recovered from the heart, liver, spleen, and lungs, at autopsy.

WINTER ASTHMA*

HENRY D. OGDEN, M. D.†

NEW ORLEANS

Respiratory allergy due to pollen is mainly of the hay fever type, and is strictly seasonal in occurrence. Bronchial asthma not infrequently occurs as a complication; especially in patients who have a more acute or extreme degree of sensitization. Some pollens appear during the winter months, such as cedar which pollinates in January and February in New Orleans. A thorough knowledge of the anthoperiods of the important anemophilous pollen is therefore essential in the proper handling of winter asthma.

In contrast to pollen, the perennial type of patient is considered to be sensitive to bacteria or to some ubiquitous inhalant antigen or antigens which are present throughout the year. Some of these cases will have clinical symptoms only during the cooler months. Again in contrast to those allergic to pollen, this group of patients has a much higher incidence of bronchial asthma. In many cases, symptoms of chronic nasal allergy are present for several years prior to the onset of bronchial asthma.

As stated above, there are many patients who have asthma only during the winter months, or who have an exacerbation of symptoms during this time. The three most important factors responsible for this seasonal variation in the opinion of the author are as follows:

1. Meteorologic conditions
2. Increased concentration of inhalant antigens
3. Infection and bacterial sensitization

METEOROLOGIC CONDITIONS

Climatic or meteorologic conditions have long been recognized as aggravating factors in asthma. There is, for instance, the asthmatic who develops symptoms only during the periods of weather change. Considerable investigative work has been done on the problem of weather and its effects on the organism as a whole, and it is obvious that climatic changes influence both mental and physical states. It has been shown by microscopic observation of capillaries that the vascular system undergoes abnormally exaggerated reactions, such as spasms or paralysis following thunderstorms or sudden changes in weather. Petersen[1] has shown that vasoconstriction is evidenced by blood pressure changes during the movement of polar air masses.

It has been claimed that coronary thrombosis is more apt to occur during periods of weather change. Weather changes have been stated to affect the autonomic nervous system, the endocrine mechanism, chemical balance (blood pH, K/Ca ratio, and protein concentration), and to even cause variations in the tolerance of various drugs. The allergic individual, who is so characteristically affected by various nonspecific influences, is bound to reflect any such profound changes.

The important factors involved in weather changes are barometric pressure, humidity, and temperature. Courtright and Courtright[2] showed that anaphylaxis in the experimental animal was easier to produce during periods of low barometric pressure. It has also been stated that skin reactions to testing (the antigen antibody reaction in miniature) is increased during periods of low pressure. However, flareup of clinical symptoms does not necessarily follow changes in barometric pressure.

The factor of increased humidity is clinically important. Many patients state that a high relative humidity is conducive to the development of asthma. Many of my patients have stated that asthma will develop when they are exposed to fog or increased moisture in air. However, some asthmatics do not seem to be influenced particularly by the humidity factor.

It is also obvious that in many individuals attacks are precipitated by temperature variations, mainly from warm to cool, and especially at the time of change of sea-

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*Presented at meeting of the Orleans Parish Medical Society, December 8, 1947.

sons. Many asthmatics whose sensitization is due to an environmental inhalant antigen will have flareups in the fall and spring. In some individuals symptoms are only present at this time. An antigen which is present in relatively small amounts may be generally tolerated by the patient, except during such periods of temperature fluctuations. In the majority of instances the fall exacerbation continues throughout the winter season, although usually of lesser degree.

Cyclonic circulation (alternating tropical and polar air masses) requires constant adjustment on the part of the individual. During the period of falling temperature (the polar air mass) sympathicotonia is present. Petersen and Vaughan[3] state that relative anoxia occurs in various areas of the body which results in smooth muscle spasm. Stimulation of local glands occurs with increased production of mucus, which then obstructs the passage of air through the respiratory tract. Excessive production of mucus is a major cause of obstruction in chronic perennial asthma, and it is in these cases particularly that we see these marked episodes associated with weather changes.

Hilding[4] has shown that in asthma goblet or goblet-like cells may be substituted for the normal columnar ciliated cells. Therefore, more mucus is secreted, which may be intimately attached to the cells. The elimination of the mucus is further hampered by the loss of cilia.

In 13 of 19 fatal cases reported by Petersen and Vaughan[3], the attacks occurred during the period of falling temperature, and death occurred in 10 during the later stage of rising temperature. They felt that in 6 cases other types of weather change were significant (change in humidity, air ionization, and wind velocity).

At the present time it seems that we must consider a combination of climatic factors, which affect the patient with an allergic background. The movement of air masses (occasionally with increased wind velocity), with resultant alteration in weather, brings with it a variety of changes. Some of these changes may not as yet be apparent. They may be magnetic or electrical in nature. It has been claimed by some that O_4 (Aran) may be connected with various physiological changes. At the present time, I consider that temperature change is the most important single cause of allergic flareups.

INCREASED CONCENTRATION OF INHALANT ANTIGENS

Another important cause of asthma in the winter months is the increased indoor concentration of inhalant antigens. Sensitization to other substances such as foods, and drugs, may coexist, and satisfactory relief may not be obtained unless these other sensitizations are recognized, and properly handled.

Allergy to house dust is the main cause of winter asthma, but allergists have long recognized that other inhalants may be incriminated to a greater or lesser degree. It is most injudicious to merely treat the winter asthmatic with house dust extract, without giving the patient the benefit of a careful allergy study. The presence of these other uncontrolled sensitizations may prevent adequate therapeutic response. As an example, I have seen a young girl, who has recently developed asthma. She gives positive reactions to house dust extract, but we have determined that her main sensitization is to coffee dust. She is employed by one of our local coffee firms and is exposed to it in her daily work.

There are, of course, many other air borne substances which may at times produce symptoms, to mention only a few: wheat flour, cottonseed, animal danders, and molds. With some of these substances, simple avoidance is sufficient, but in the case of others this is practically impossible. In these individuals hyposensitization with the offending antigen is often indicated. All cases should be given specific instructions concerning those substances to which clinical sensitization can be demonstrated. A positive skin reaction may not be sufficient proof that allergy exists to any suspected material. In other words antibodies in the skin do not prove that the reacting substance is producing symptoms in the

shock organ. The allergist appreciates these problems, and the proper evaluation of each case requires careful study, and a knowledge of possible misleading factors. Therefore, anyone interested in allergy must be able to recognize various exposures and contacts which may be of clinical significance. Also, while sensitizations may be multiple, one may be primary and another secondary, (i.e. of an occasional aggravating nature).

It is perfectly obvious that the indoor concentration of these antigenic substances is increased during the cooler months. It must be remembered that house dust is a decomposition product of various fabrics and substances. In cooler weather, heavier clothes are used, and the windows are closed. Rugs, blankets, and window drapes add to the atmospheric concentration. In the fall, clothes are brought out which have been stored during the warmer months, and may contain a considerable amount of dust. In a survey of 140 patients allergic to house dust, I found that all proven cases showed manifestations in the winter season.

This seasonal change in clothing and household furnishings is more apparent in a subtropical area such as New Orleans. It gives a suddenly added antigenic burden during this time, which imparts a definitely seasonal characteristic to these inhalant sensitizations.

INFECTION AND BACTERIAL SENSITIZATION

The third important factor responsible for this seasonal variation is bacterial sensitization, which commonly occurs in respiratory allergy. Since respiratory infections are more common in the winter months, this problem requires careful consideration.

All cases of respiratory allergy may be shown to fall into one of the following groups:

a) Noninfective. This group includes those cases who can be shown to be allergic to pollens, foods, and various inhalant substances. In the older classifications they would be labeled "extrinsic". In this type we usually see immediate whealing or urticarial reactions on skin testing.

b) Infective. Here skin reactions are either completely negative, or of no clinical significance. Acute or chronic infections of the respiratory tract are recognized to be of great importance. Exacerbation of symptoms may occur in a flareup of such an infection. The "intrinsic" variety falls into this group. In the true "intrinsic" type of patient, the symptoms are perennial in nature, and show no seasonal variation. There are on the other hand other "infective" cases whose symptoms flare up in the winter coincidental with the presence of acute respiratory infections.

c) Infective and noninfective. Here we have a combination of (a) and (b). In this group clinical allergy to extraneous antigens may be demonstrated with the superimposed factor of bacterial sensitization. It is becoming more apparent that a very large number of cases of the "noninfective" group will show varying degrees of an "infective" component.

The problem of bacterial allergy has received a great deal of discussion. It is felt that there are two main varieties, the atopic and the tuberculin types. In the first variety immediate whealing reactions may be seen on skin testing, while in the latter delayed skin reactions are characteristic. When infection is a cause of respiratory allergy, the sensitizing organisms may at times be found in the paranasal sinuses. These organisms are predominantly of the Gram positive type. In a series of cultures (mainly obtained from antral irrigations) we found that one or more Gram positive organisms (usually staphylococci) were recovered in 52 of a total of 55. Other Gram positive organisms were found in many of them. Cultures of Gram negative organisms alone were found on only three occasions. Vaccines made from these cultures were used in many patients, often with apparent benefit.

In another study with Evans and Kelly[5] diptheroids were found in an unusually high percentage. Cultures here were mainly from nasal swabs, and incubation was carried out for seven days in a very rich media.

Therefore, the sulfonamides and antibiotics have a definite place in our armamentarium. The value of penicillin by injection or by inhalation is well known. In a controlled study, using 179 patients, I found that the nasal use of tyrothricin did not lessen the amount of allergic manifestations during the cooler weather. In another controlled study[5] we found that the nasal use of bacitracin possibly decreased the amount of allergic symptoms in some patients.

CONCLUSION

Asthmatics are prone to become worse during periods of weather change, especially when the temperature is falling. In addition to the winter months, this is especially noticeable during the change of seasons in the fall and spring. The added burden of increased indoor concentration of inhalant antigens must be considered. Infection of the respiratory tract may aggravate asthma, and this factor is of distinct importance during the winter months.

REFERENCES

1. Petersen, William F.: Man-Weather-Sun, Charles C. Thomas, Springfield, 1947.
2. Courtright, L. J., and Courtright, A. B.: Inhalant sensitization and shock in guinea pigs under controlled atmospheric conditions. J. Allergy, 16:146, 1945.
3. Petersen, W. F., and Vaughan, W. T.: Weather and death in asthma. J. Allergy, 15:97, 1944.
4. Hilding, A. C.: Relation of ciliary insufficiency to death from asthma and other respiratory diseases. Tr. Am. Acad. Ophth. (1942) 47:376, 1943.
5. Ogden, H. D., Evans, F. L., and Kelly, J. D.: Nasal use of antibiotics in respiratory allergy. To be published.

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TREATMENT OF CONGENITAL GLAUCOMA WITH BETA RADIATION

REPORT OF A CASE

GEORGE M. HAIK, M. D.
LOUIS A. BREFFEILH, M. D.
AND
J. E. BOGGESS, M. D.*

NEW ORLEANS

On October 31, 1946, a 5 year old white male was seen in the Pediatric Clinic of Charity Hospital and referred to the Ophthalmology Department with a diagnosis of glaucoma and cataracts.

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When seen in the clinic the history obtained from the mother was that the child's eyes had seemed larger and whiter than normal since birth. She had noticed that the child could not see well, but the degree of the impediment could not be determined.

Examination revealed a well-nourished, well-developed, white male not appearing ill, but with evidently deficient vision. The child was very curious about objects around and seemed above normal in acuteness and energy. When examining an object it was held close to his eyes and his head was tilted to the left.

External examination of the eyes revealed that they were larger than normal, the cornea seemed particularly large, and the anterior chambers were deep. The cornea of the right eye was diffusely translucent and the left eye contained patchy opacities. The iris of the right eye was only hazily seen and the pupil reacted sluggishly to light and accommodation. The iris and pupil of the left eye were normal.

Funduscopically only a pink reflex was obtained in the right eye. The left fundus was not seen distinctly, though the disc was distinguished and some of the vessels were seen. Tension was obtained with the 10 grain weight only and was 48 for the right eye and 55 for the left eye.

The rest of the physical examination and all laboratory tests were essentially negative.

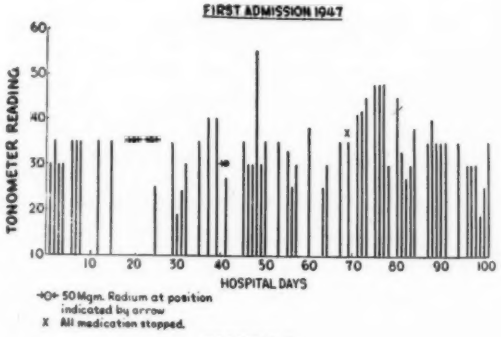

FIGURE 1

The impression of buphthalmos was gained and the child was admitted to the hospital. Pilocarpine, 2 per cent, four times a day to each eye was started. On Novem-

ber 11, an Elliot's trephine was performed on the left eye and on the 18th an identical procedure was carried out on the right eye. Carcholine, 1½ per cent in 1:3000 zepharin, was ordered postoperatively every four hours to both eyes. Within three days the right eye developed marked ciliary injection, lacrimation, and photophobia. The tactile tension in the right eye was elevated but seemed lower than that of the left eye, which was markedly elevated. The cornea of the right eye was hazy. The pupil was about 8 mm. in diameter. A large knuckle of iris and ciliary body was prolapsed into the filtering bleb in the right eye.

On December 2, 5 cc. of sterile milk were given and atropine 2 per cent ordered four times a day to the right eye, along with hot, moist compresses. A moderate rise in temperature was obtained but the eye continued to grow worse so that an enucleation was performed on the right eye and an acrylic resin implant was used. Massages were started on the left eye on December 14. The patient was discharged from the hospital on December 20.

A pathological report on the right eye was as follows:

Cornea: An open penetrating wound was present at the left limbus. The opening was partially blocked by organizing connecting tissue and the dislocated lens. The epithelium was irregular and on the right was covered by this connective tissue layer. Bowman's membrane was absent and replaced by wandering connective tissue cells. The anterior chamber was very deep and many pigment-filled macrophages were present on the endothelium and in the trabecular meshwork. An iridectomy was present on the left, with a remnant of a tip of iris adherent to the anterior surface of the lens. On the right the iris showed chronic inflammatory reaction with plasma cells and lymphocytes.

Limbus: The left limbar area was involved in the wound but on the right the angle was widely open. Serial section showed the meshwork to be poorly formed and Schlemm's canal to be absent or faulty.

Ciliary Body: The ciliary body was prolapsed on the left. On the right there was chronic inflammatory reaction.

Choroid: Choroid was detached in the anterior half of the globe by massive hemorrhages. Plasma cells and lymphocytes were present and there was a massive infiltration of eosinophiles. These cells were present in the inner layer of the sclera but did not involve the emmisaries.

Retina: The retina was totally separated by subretinal hemorrhage. There was a disinsertion at the ora on the left.

Optic Nerve: The disc showed bowing and glial proliferation.

Lens: Dislocated and adherent to the wound on the left. It was covered on the posterior surface by detached vitreous which contained red blood cells and macrophages.

Diagnosis:
1. Hydrophthalmos.
2. Perforating wound, surgical
3. Dislocated lens.
4. Detached choroid and retina due to hemorrhages.
5. Glaucomatous cupping of the disc.
6. Chronic uveitis.

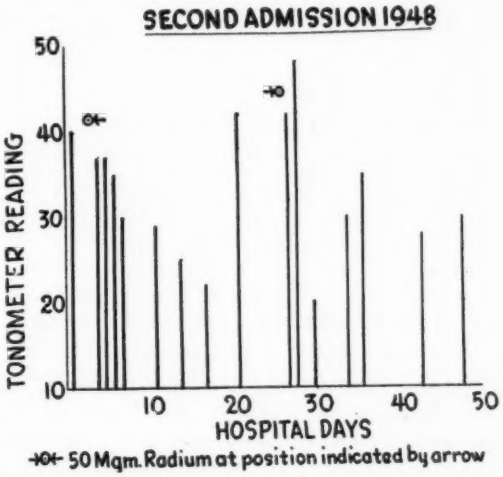

FIGURE 2

On September 13 the patient was seen again for the first time since his discharge, and readmitted to the hospital for further observation. The tension in his left eye was 30 on admission. Prostigmine 2½ per cent and pilocarpine 2 per cent were alternated six times a day until September 22, on which day the dosage was increased to instillation of each of the drugs five minutes six times a day.

This was the only treatment until October 2, when the first application of radium was given. With a 50 mgm, placque of radium, firm pressure was made on the anesthetized eye over the ciliary body at 9 o'clock for ten minutes. This was then repeated over the ciliary body at 3 o'clock. On October 6 this was repeated. Tensions

were taken practically every day (See Figure 2). Severe hyperemia developed following the last application. This reaction had begun to subside when the third application was given. This consisted of ten minutes over the limbus at 9 o'clock. Following, hyperemia again became severe and persisted for about three weeks. On November 9 there was noticed atrophy of the vessels in areas about 6 mm. in diameter at the points of radium therapy. On November 20, all miotics were stopped in order to observe effects of the radiation. The patient was discharged on December 22, 1947.

The patient was readmitted on January 3, 1948, and on January 5 beta radiation was given for ten minutes over the ciliary body at 3 o'clock. A gonioscopy was attempted on January 26 but the opacity of the cornea prevented visualization of the angle. On January 28, beta radiation was given to the ciliary body at 9 o'clock for twenty minutes. The patient was observed for a bout a month and then allowed to go home.

DISCUSSION

Congenital glaucoma is defined by Duke-Elder as a structural abnormality in the region of the angle of the anterior chamber, offering an obstruction to the drainage mechanism for intra-ocular fluids, so that pressure of the eye is raised, and since the coats at this stage are plastic, the while globe becomes enlarged.

Originally all forms of congenital glaucoma were classified as buphthalmos but recently cases have been divided into two groups:

1. Hydrophthalmia is the name applied in those cases in which there is either an actual or apparent absence of the canal of Schlemm.

2. Buphthalmia is a condition in which there is an anomaly of the mesoderm at the corneoscleral junction resulting in a persistence of the prenatal condition wherein the trabeculae are not opened up.

Anderson examined and found the canal of Schlemm in 75 per cent of the earliest specimens[2]. He also found no evidence of the canal in one-half of the specimens taken from children over 2½ years of age, and he feels this absence was due to its closure by the distended eye and its increased intra-ocular pressure.

This patient, upon admission, presented a difficult problem as tension was sufficiently high to cause the enlargement and engorgement described. A gonioscopic examination could not be made at the time and medical treatment was instituted, but it failed to control the tension. Surgery was considered and an Elliott trephine was made on both eyes. Due to thinning of the coats, difficulty was encountered but since the operation could be done satisfactorily it was attempted on the second eye and resulted in the loss of same. An iridotasis or iridencleisis should have been the surgery of choice and is the one preferred at the present time as it entails less complications.

The histological specimen was diagnosed as hydrophthalmia with an absence of the canal of Schlemm, either actual or apparent, and we may assume a similar condition is present in the other eye. The remaining eye continued to show increased tension and cyclodiathermy was considered but due to the thinness of the sclera and ciliary body and the complications which may result in a one-eyed individual, other measures were searched for and none were considered satisfactory for this individual case.

At the same time the effect of beta radiation on the ciliary body of rabbits was being studied by the Department of Ophthalmology. Although the experiments were not completed, information had been obtained which indicated that the destruction of the ciliary body was sufficient to control the formation of aqueous. It was decided that beta radiation could be used on this case and it was applied over the ciliary body at 9 and 4 o'clock for ten minute periods, using the Iliff applicator which contains 50 milligrams of radium screened by 1/10 mm. of monel metal. A total dosage of fifty minutes at 9 o'clock and thirty minutes at 3 o'clock was used.

The mechanism by which the formation of aqueous was controlled by destruction

of the ciliary body will be found in a full detailed report soon to be published in the American Journal of Ophthalmology by Haik, Breffeilh and Barber under the title "Beta radiation as a possible therapeutic agent in glaucoma; experimental studies and report of a clinical case."

In the treatment of congenital glaucoma Duke-Elder wrote, "The treatment of congenital glaucoma is full of disappointments and frequently quite ineffectual. Some cases, it is true, become arrested, a few respond to treatment but absolute glaucoma and ultimate blindness is the usual end result."

Only those cases of buphthalmia may be offered some hope as goniotomy operation as advised by Burkan has proven successful in 66 cases and unsuccessful in 10 cases.[3]

At present we are not certain of the dosage needed to produce desired results but experiments indicate one hour of radiation in ten minute periods will produce the desired changes. Immediate results are not expected, as it takes time for tissue to react.

Further treatment may be indicated in the case reported here; at present all medication has been discontinued and the tension has remained fairly stable. As to the final results, all indications point to improvement in an otherwise hopeless case.

The latest tonometer readings taken in the clinic on a weekly basis are:

March 2 Schiotz 32 mm.
March 9 Schiotz 29 mm.
March 23 Schiotz 13 mm.
March 30 Schiotz 29 mm.
April 6 Schiotz 26 mm.
April 13 Schiotz 32 mm.
April 27 Schiotz 27 mm.
May 5 Schiotz 27 mm.

REFERENCES

1. Duke-Elder: Textbook of Ophthalmology, Vol. II and III.

2. Anderson, J.: Hydrophthalmia or Congenital Glaucoma, Cambridge University press, 1939, p. 151.

3. Barken, Otto: Technic of goniotomy for congenital glaucoma, Tr. Am. Acad. Ophth., Jan.-Feb. 1948, p. 210.

4. Haik, G. M., Breffeilh, L. A., and Barber, Aeleta: Beta radiation as a possible therapeutic agent in glaucoma; experimental studies and report of clinical case, Am. J. Ophth. In Press.

ACUTE PULMONARY TUBERCULOSIS

REPORT OF A CASE SUCCESSFULLY TREATED BY LOBECTOMY AND DIHYDROSTREPTOMYCIN

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There is little in medical literature concerning treatment of caseating pulmonary tuberculosis of the right lower lobe with lobectomy and adjunctive use of dihydrostreptomycin both preoperatively and postoperatively.

It is stated that primary lobectomy is preferable to thoracoplasty when cavities are situated in the basal portion of the lower lobe and the active tuberculous process is limited to the lower or middle lobe.[1] Review of the current literature, however, does not include the simultaneous use of dihydrostreptomycin with this procedure.

The following case is reported because of the striking and dramatically rapid result obtained.

CASE REPORT

A 16 year old white male was admitted to Hotel Dieu, New Orleans, Louisiana, on January 19, 1949. For four years the patient had diabetes which was well controlled by 25 units of protamin zinc insulin daily. On January 13, 1949, the patient suddenly developed a high fever (101.6° F.) followed by an acute, severe pulmonary hemorrhage. He was seen by his physician in Picayune, Mississippi, who gave him 300,000 units of penicillin. However, the patient continued to run a febrile course and hemorrhaged twice the following day, each time expectorating about a cupful of bright red blood. He was admitted to The Picayune hospital on January 15, 1949, at which time 75,000 units of penicillin were administered every three hours and 0.5 gram of streptomycin every six hours. He became afebrile on January 17, 1949, but on January 18, 1949, another severe pulmonary hemorrhage occurred. During this time the patient received 80 to 90 units of insulin daily and was on a 1500 calorie diabetic diet. On January 19, 1949, the patient was sent to the Hotel Dieu Hospital. The history revealed that since approximately November 1, 1948, the patient had been coughing. The cough was only occasionally productive of greenish sputum, which was not foul smelling. There was also history of frequent coughs during the past six months which were of brief duration. There had been no weight loss or excessive fatigue. Two weeks before the onset of the present illness, he had an attack of chills and fever which quickly subsided. There was occasional substernal dull

pain after coughing. A persistent frontal headache had been present since the onset of the present illness. The patient was a high school student of normal intelligence who stated that he had been well all of his life except for diabetes mellitus, which was well controlled. A chest x-ray had been taken two years ago and reported negative. He had been knocked unconscious about a month before admission while playing basketball but suffered no harmful after effects. There was no family history of tuberculosis.

Physical Examination: The patient was a well developed, 16 year old, white male appearing very pale, apprehensive and acutely ill. On admission his temperature was 99.6°, pulse 70, respiration 20, and blood pressure 95/60. He was six feet one inch tall and weighed 128 pounds (58 kg.). The physical examination was essentially normal except for the chest findings. There was slight diminution in intensity of the breath sounds over the right middle and lower lobes, with dullness on percussion noted over this area. An occasional fine crackling râle was heard over the right lower lobe which persisted after coughing. There appeared to be a slight deficiency in expansion of the lower half of the right chest.

Laboratory Findings: The roentgenogram showed a cavity situated posteriorly at about the midlevel of the lower lobe. There was considerable interstitial infiltration surrounding the abscess. Admission laboratory work revealed an RBC of 4,900,000 with 13.2 grams of hemoglobin. The WBC was 9,700 with 2 eosinophiles, 6 stabs, 52 segmenters, 28 lymphocytes and 12 monocytes. The color index was 0.9. Urinalysis was negative except for a trace of sugar. There was no acetone. The NPN was 26 mg. per cent, and the blood sugar was 324 mg. per cent. The sedimentation rate was 30 mm. in an hour. Initial sputum examination revealed no acid fast organisms. It was not until the sixth sputum examination that many acid fast bacilli were demonstrated, but they appeared on all subsequent sputum examinations. At this time the patient was started on penicillin, 50,000 units every three hours, dihydrostreptomycin, 15 grams every 12 hours, and a 1,610 calorie diabetic diet. He was given protamin zinc insulin, 25 units, each morning. His urine was checked before each meal, and regular insulin given accordingly. He was placed in postural drainage before the sputum examination became positive. The blood sugar gradually dropped to normal limits, and the urine became free of sugar. On January 31, 1949, the patient was seen by Dr. George Taquino. Using pontocaine to spray the throat and hypopharynx and 10 per cent cocaine in the pyriform fossae and in the trachea, a bronchoscopy was done. The mucous membrane of the right lower lobe bronchus was extremely thickened and highly inflamed. The rest of the bronchial tree was apparently normal. Tubercle bacilli were found in the bronchial secretions.

The patient became afebrile and began to feel and look much better. His diabetes was well under control. On February 2, 1949, a surgical consultation was requested, and it was the opinion of the consultant, Dr. F. F. Boyce, that in view of the findings of positive acid fast sputum with cavitation in the right base and the repeated pulmonary hemorrhages earlier, a lobectomy was indicated.

Surgical Procedure: The patient received multiple blood transfusions, and his diet was increased to 3000 calories supplemented with vitamins. On February 7, 1949, a right lower lobectomy was done. The right lower lobe was infiltrated with nodules and contained an abscess filled with caseous appearing material which was opened during separation of the lower lobe from the middle lobe. It was noted at the time of operation that there was minimal tubercular involvement of the middle lobe of the right lung. It had appeared from x-ray that only the right lower lobe was involved. The right upper lobe appeared perfectly normal. The patient received blood during the operation. The blood pressure was maintained above 100. The patient left the operating room in good condition.

The pathological report was as follows: Gross description. The specimen consisted of a lower lobe of lung weighing 375 grams measuring 15 by 12.5 by 6 cm. It was nodular and firm. The pleural surface was roughened by old adhesions. On section there was nodular caseating tuberculosis involving the entire lobe. The nodules were confluent to form masses up to 1.3 cm. in diameter. Under the lateral pleural surface was a 4 cm. old thick walled cavity filled with clotted blood, smaller caseous filled cavities were found up to 1.5 cm. in diameter. An opened, partially emptied, 2 cm. cavity was present in the upper portion of the lobe. Semicaseous material was seen in some of the smaller bronchioles. The second order bronchi showed gross ulceration. Microscopic diagnosis: Caseating nodular pulmonary tuberculosis with recent and old cavitation. The intervening pulmonary tissue showed fibrosis.

Clinical Course: The patient had an uneventful postoperative course. The temperature rose to 101° F. on the first postoperative day, rapidly returning to normal, and the patient was afebrile from that point on. The patient was in an oxygen tent for one week postoperatively, received blood, glucose, and saline infusions and was continued on penicillin and dihydrostreptomycin as before. His diabetes was well controlled by giving insulin to scale for the first four postoperative days, and then by giving regular insulin, 30 units, and protamin zinc insulin, 15 units, every morning. All sputum examinations, gastric washings, and

urines were negative for acid fast organisms after the operation. The sedimentation rate returned to normal. He was discharged greatly improved on the thirteenth postoperative day. He was sent home, where he received 0.5 gram dihydrostreptomycin twice a day. The patient was seen again on March 21, 1949, at which time a chest x-ray showed some elevation of the right diaphragm and some pleural reaction along the periphery. The right lung appeared well aerated. The left lung remained clear. The patient looked and felt well and had gained five pounds. All the chest findings were completely normal and sputum examinations were negative for acid fast. Dihydrostreptomycin was reduced to 0.5 gram daily at this time.

On April 23, 1949, an x-ray revealed a normal chest. The patient had returned to school, felt excellent and had gained 15 pounds since his discharge from the hospital. Physical examination was completely normal. Dihydrostreptomycin was discontinued at this time. There had been no signs of any toxicity to the dihydrostreptomycin.

COMMENT

It is still too early to draw any definite conclusions from this particular case, but the change in this boy's condition within a period of one month was startling. The amazing clinical improvement along with the normal chests x-rays, repeated negative sputum examinations, and the absence of of physical findings permits the diagnosis of arrested tuberculosis.

Close observation will continue at least another year. In the meantime, the patient has progressed from an acutely ill individual to a healthy young man who has completely resumed his interest in normal social pursuits. Because of the unusual nature of the tuberculous lesion and the dramatic response to surgery and to dihydrostreptomycin, I feel that this case should prove encouraging in cases of similar nature where a lobectomy combined with dihydrostreptomycin therapy might offer prospect of improvement in spite of the fear of dissemination.

REFERENCE

1. Maier, Herbert C.: Lobectomy and pneumonectomy in pulmonary tuberculosis, Am. Rev. Tuberc., 58:576, (November) 1948.

BRUCELLOSIS WITH JAUNDICE*

REPORT OF A CASE

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It is now well established that brucella infection in man may masquerade under any of its numerous atypical clinical expressions. Hall[1] mentions the nonspecificity of symptoms and signs and states that dependence on laboratory tests is sometimes wrought with diagnostic confusion. The occurrence of jaundice in brucellosis has been encountered by previous authors. Harris[2] mentions in his textbook a case with jaundice and clay colored stools reported by Green, and states that he has observed moderate jaundice in several patients. Parsons and Poston[3] in a most exhaustive necropsy report describe a mechanical obstruction produced by enlarged lymph nodes at the hilum of the liver, which resulted in great dilatation of the bile canaliculi with tremendous round cell infiltration in all portal areas and considerable fibrosis. This could be explained on the basis of obstruction with perhaps an ascending infection. Gall bladder infection by the brucella organism and the recovery of the organism by duodenal drainage are mentioned by Harris[2] and deserve clinical attention.

A case report of obstructive jaundice due to brucella infection is herein reported. We believe it of interest not only because it explains the pathogenesis of the jaundice, but also because of the masquerading nature of the infection. The presentation will be given in a chronological order as nearly as possible.

CASE REPORT

A white male, 45 years of age, was admitted to the Mercy Hospital on December 20, 1947, to be studied regarding the etiology of jaundice of two weeks' duration. The history of his illness began approximately four weeks before admission, with anorexia, belching, and upper right quadrant dis-

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comfort. Two weeks later he noticed that his urine was darker than usual and the stools lighter in color. Shortly thereafter a yellow discoloration of the eyeballs occurred. About this time the patient began to have chills and fever, mainly in the evening, accompanied by rather profuse sweats and marked weakness. The patient was given a course of penicillin and because of its ineffectiveness sulfadiazine was substituted, which likewise failed to abate the symptoms. In the meantime the stool had become clay colored and there was complete loss of appetite.

The patient gave no past history of jaundice or of any other recent illness. The family history was irrelevant. The patient, a fur buyer, resided in Lockport, a town in South Louisiana approximately 40 miles west of New Orleans. The chief means of livelihood in the locale are farming, trapping, and fishing. While the patient knew of no ingestion of contaminated milk, dairy products, or water, the fact remains that brucellosis is endemic in Louisiana and much raw milk is consumed in the rural parts of the state.

Physical examination revealed a well developed and nourished white male adult, with a ruddy complexion and moderate degree of jaundice of sclerae and skin. The blood pressure was 120/85, temperature 101.5° F., and pulse rate 80. The liver edge was palpable about one finger's breadth below the costal margin and was slightly tender. First percussion over the liver posteriorly also elicited some tenderness. The epigastric region was slightly tender and offered slightly increased resistance to the palpating hand. The spleen could not be felt and no superficial glandular adenopathy was detected. The diagnosis of infectious hepatitis was considered tentatively as most likely at this point.

Laboratory data revealed a total white blood count of 6,000, with 49 per cent lymphocytes, 47 per cent neutrophils, and 2 per cent monocytes. The red cell count was 4.8 million with 14.5 grams of hemoglobin. The urine was positive for bile, and urobilinogen was present in a dilution of 1:5. The icterus index was 28, cephalin flocculation 1 plus in forty-eight hours, and the thymol turbidity 1.8 units. The qualitative van den Bergh gave a delayed direct reaction. The one minute serum bilirubin was reported as a trace, with 3 mgm./100 cc. total serum bilirubin. The stool was positive for urobilinogen, but otherwise negative for ova, cysts, and parasites. The blood chemistry was normal and blood Wasserman negative.

The laboratory findings suggested an extra hepatic type of jaundice rather than a hepatocellular type (infectious hepatitis). A short (six hour) G. I. series was done which demonstrated a rather prominent persistent deformity of the first portion of the duodenum, very suggestive of an enlarged gall bladder (Figure I). Gall bladder visualization study, after the jaundice had subsided, failed to visualize this organ.

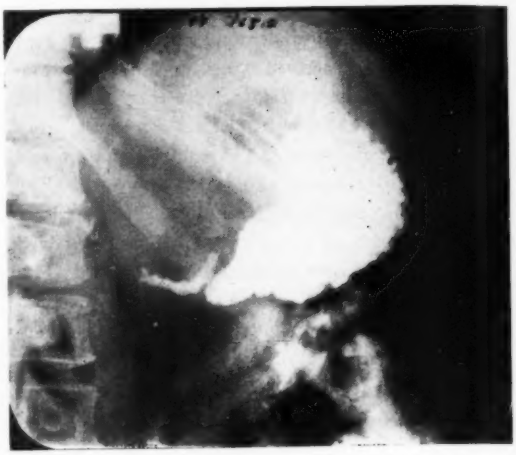

Figure 1. Note the large pressure defect on the superior aspect of the duodenum which is suggestive of gallbladder pressure.

Clinical Course. The temperature remained elevated for three days, ranging from 101.5° on the day of admission to 99.5° on the third day, followed by normal temperature thereafter. The jaundice rapidly subsided, and on the eleventh day the icterus index had fallen to 12. With the subsidence of the jaundice, the patient's appetite improved and he became entirely asymptomatic. The urine and stool became normal in color. A repeat six hour G. I. study showed the pressure deformity previously seen to be unchanged. Thus far the patient had received no special medication, but had been placed on a high protein, high carbohydrate, high vitamin diet.

The diagnosis now became that of incomplete obstructive jaundice. The explanation we felt lay between a silent calculus not visualized by x-ray, and bilitary tract malignancy. Upon request of the patient, he was allowed to return home on December 31, 1947, in order to attend to some important personal matters, and was instructed to return in two or three weeks.

The patient remained at home the greater part of the following month, during the last week of which he had a low grade fever (99-100°), mild weakness and sweating, and, according to his local physician, a recurrence of mild jaundice. Penicillin was administered until the patient could return to the hospital. When he was readmitted on January 25, 1948 he was afebrile and asymptomatic except for a slight discomfort in the right upper quadrant. Another G. I. series on January 27, 1948, showed the same duodenal deformity (Figure 2.) Laboratory data at this time revealed a white blood count of 7,000 with 54 per cent lymphocytes

Figure 2. G. I. series, taken 24 hours after attempted gallbladder visualization with double dose of priodax, demonstrates a vague gallbladder shadow immediately adjacent to the still persistent deformity. (Gallbladder failed to visualize on the previous day.)

and 46 per cent neeutrophils. The icterus index was 10, and a bromsulfalein test showed no retention of the dye at the end of fifteen minutes. Thymol turbidity was 2. 2 units. The urine was negative for bile or urobilinogen.

At this point the findings seemed to us to indicate that we were dealing with a case of incomplete obstructive jaundice. Although there was no evidence of obstruction on readmission to the hospital, the duodenal deformity remained roentgenologically the same. The exact cause of the obstructive phenomena and x-ray findings still eluded us. Consultation with a surgeon was had, and he agreed that exploration was indicated and voiced an opinion that the patient had either biliary tract malignancy or gall bladder disease with silent stones.

On February 2, 1948, the patient was subjected to an exploratory laparotomy. The following, as described by the surgeon, was found: The gall bladder was moderately distended. The cystic duct was of normal size. The wall of the gall bladder was slightly thickened but of normal color and no stones were palpable. The common duct was moderately dilated. The hepatico-duodenal ligament was markedly thickened, mainly in the outer third, caused by enlarged lymph nodes along the posterior and anterior aspects adjacent to and superimposed upon the common bile duct. These extended from the common hepatic duct all the way to the ampulla of Vater posteriorly. Anteriorly the lymphadenopathy extended from the portahepatis to the duodenum. Grossly the liver showed evidence of interstitial hepatitis. The left lumbar gutter and occasional places in the mesentery of the small bowel contained enlarged lymph nodes. The head of the pancreas was soft and revealed no induration. The stomach and duodenum showed no evidence of ulceration, malignancy or thickening. The glands anteriorly and posteriorly along the common bile duct were completely dissected away. Further examination then revealed that there existed no other abnormality of the extra hepatic-pyloric apparatus.

The operative opinion was inconclusive, since grossly the glands did not appear neoplastic and Hodgkin's disease seemed an unlikely possibility. It was concluded from the operative findings that whatever the cause, the obstructive phenomena were due to pressure on the common duct by the enlarged lymph nodes. Hence final diagnosis we hoped would come from the pathologic study of the removed glands.

While there was no preoperative febrile reaction, there occurred postoperatively a sudden elevation of temperature ranging from 103° to 100°, lasting three days and accompanied by profuse sweating. Thereafter the postoperative course was uneventful and the patient was entirely free of symptoms upon discharge on February 13, 1948.

Extremely interesting was the report of the pathologist, and for this reason it is incorporated in its entirety: The biopsied glands showed numerous small circumscribed discrete and conglomerate areas consisting of cells resembling endothelial cells. These were irregularly arranged and showed no definite pattern. The reticulum cells showed moderate hyperplasia, and areas of chronic inflammation and pyknosis were seen. The histological diagnosis was that of a granulomatous lymphadenitis. Upon the basis of his findings the pathologist suggested that serologic test for brucellosis be made. This was done and two successive agglutination tests for brucellosis revealed a positive reaction at a titre of 1:640 for *B. abortus*. Likewise two blood cultures were carried out under "special technic." Both cultures were reported negative. A skin sensitivity test for brucellosis was made subsequent to the two agglutinations and was found 3 plus positive. The failure to carry out cultural studies of the glands, we feel, at least under the circumstances is forgivable.

The patient was last seen on June 11, 1948, at which time he was still asymptomatic. A repeat G. I. series at this time showed a significant decrease in the duodenal deformity (Figure 3), and a repeat agglutination test showed an increased titre of 1:1280. Examination of this date revealed a palpable, nontender liver edge, and at the site of the previous skin test there remained a prominent depressed scar about 0.5 cm. in diameter. Verbal communication with his local physician reveals that the patient remains entirely symptom free ten months after the operation.

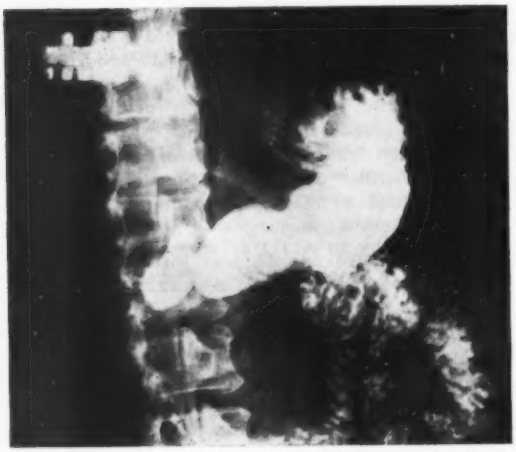

Figure 3. Demonstrates a significant lessening of the deformity five months postoperatively.

COMMENT

We readily admit that this case will have to be added to that group of patients with acute brucellosis in whom useless surgery was performed.[4, 5] However, we accept the term "useless" only as it refers to the failure of or need for surgical intervention in favorably altering the course of illness. Though seemingly paradoxical, in retrospect, we think surgery was indicated. Assuming agglutination and skin tests had been included in the study of the patient and the positive results of course obtained, what then would have been done? Much discussion and deliberation would have ensued, since we would have been confronted with both a therapeutic and, in part, a diagnostic problem. Would the diagnosis of acute brucellosis have satisfied the entire clinical expression in this case? Would we have been willing to visualize the pathogenesis as that of lymphatic glandular adenopthy which, by means of pressure encroachment, was causing the obstructive and duodenal deformity? Our answer we feel certain would have been no. If the possibility of a silent biliary calculus had been the only other condition to be considered, postponement of surgery would not only have been justifiable, but indicated. On the other hand there would have remained the possibility of biliary tract malignancy, which has in the past defied our diagnostic acumen and often still does. It might then have been assumed, on the basis of the agglutination titre, that this patient, who lives in a region where brucellosis is endemic, might have had infection in the past, or, if the increasing titre had been detected, that he might possibly be the victim of two diseases.

While we claim no benefit resulting from surgical removal of the obstructive agent, we feel sure no harm was done, and the doubt of more serious pathology was removed. Finally, we admit that as things actually stood prior to surgery, without its help the diagnosis of brucellosis might have continued to remain unsuspected in this case.

REFERENCES

1. Hall, W. H.: Brucellosis: Clinical aspects. Minnesota Med. 29:679, (July) 1946.
2. Harris, H. J.: Brucellosis, Clinical and Subclinical. 2nd edition, 1941, Paul B. Hoeber, Inc., New York.
3. Parsons, P. B., and Poston, M. A.: The pathology of human brucellosis: Report of four cases with one autopsy. South. M. J. 32:7, (Jan.) 1939.
4. Simpson, W. M.: Undulant fever (brucellosis). J. Indiana M. A. 27:564, 1934.
5. Simpson, W. M.: The clinical picture of undulant fever. Ohio State M. J. 27:21, (Jan.) 1931.

THE TREATMENT OF INFLAMMATORY DERMATOSES WITH ORAL BISMUTH*

(SODIUM BISMUTH TRIGLYCOLLAMATE)†

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Bismuth has been one of the principal drugs used in the treatment of syphilis for many years. Although its spirocheticidal index is lower than trivalent arsenic, it was relatively a safer drug. The parenteral route was the usual mode of administration, except for an occasional intravenous injection of certain aqueous bismuth compounds. No satisfactory form of bismuth for inunction has ever been perfected. A safe, therapeutically satisfactory, oral form of bismuth that was well tolerated had not been

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†Tablets furnished by Carroll Dunham Smith Pharmacal Company, New Brunswick, N. J.
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forthcoming until sodium bismuth triglycollamate, known commercially as "Bistrimate," was introduced.

The original clinical investigation with this drug was conducted to determine the value of the oral form of bismuth in the treatment of all stages of syphilis. In the course of the investigation, quite by accident, and at the suggestion of various persons, certain nonspecific, inflammatory dermatoses were included in the scope of the investigative work to determine the response of these dermatoses to bistrimate.

Subsequent reports on the clinical studies of bistrimate have been given by Howles,[1] Gross,[2] and others[3, 4, 5] in the treatment of various dermatoses. The study on the use of oral sodium bismuth triglycollamate has been continued in the treatment of all stages of syphilis, including cutaneous, visceral, and that of the central nervous system. Bistrimate was used only and in combination with other antisyphilitic measures, but this report is limited to the use of this oral form of bismuth in the treatment of several inflammatory dermatoses.

At first, bistrimate was used only in those dermatoses in which parenteral bismuth had been used and recommended in treating the particular eruption. Because of the low toxicity of this form of bismuth, many inflammatory dermatoses and some noninflammatory types have been added to the list of skin conditions to be included in the study.

The clinical material used in this study was obtained from the Dermatology Clinics of Charity Hospital and from the private practice of the author and his associates.

Sodium bismuth triglycollamate[6] is a bismuthyl salt of triglycollamic acid combined with three equivalents, disodium triglycollamate, to form a double saltlike structure. The molecular weight is 1142 and the bismuth content is 18.3 per cent. Sodium bismuth triglycollamate occurs as a white powder which dissolves readily in water, to give a solution which is approximately neutral in reaction. Solutions of sodium bismuth triglycollamate are stable from a Ph of 2.8, to a Ph of 10.0, and not precipitated by the ions found normally in the body fluids, such as phosphate and chloride. Each tablet contains 410 mgms. of sodium bismuth triglycollamate, equivalent to 75 mgms. of metallic bismuth.

The pharmacological and chemical studies of bistrimate were carried on by De Graff[10] and associates. The studies on bistrimate have shown that the drug is adequately absorbed from the gastrointestinal tract with relatively little local irritation and is rapidly and completely excreted in the urine. Animal experimentation with analysis of the liver and kidney tissue showed that an accumulation of bismuth, after the oral administration of bistrimate, is no greater than that following the parenteral preparations. The available evidence indicates that any toxic effects produced by the drug are those referable to the systemic action of bismuth. This has proved that the triglycollamic acid form of bismuth is another, and apparently a very satisfactory, means of administering bismuth which has a desirable index of absorption.

Bistrimate, when administered to man in doses equivalent to 300 to 450 mgms. of metal per day, will produce a daily urinary excretion level of bismuth which usually exceeds the 2 and 4 mgm. per day considered necessary by Cole and co-workers,[5] for the useful antisyphilitic agent. It has been shown that under these conditions the drug is well tolerated over a period of continuous therapy, as long as a year.

This report contains only cases of dermatoses not included in the previous report presented by Gross,[2] and the author at the American Medical Association meeting, June 1947.

CHART I

COMPILATION OF CASES TREATED WITH BISTRIMATE

Verruca	69
Lupus Erythematosus	69
Vitiligo	56
Lichen Planus	39
Sarcoidosis	11
Granuloma Annulare	9
Plantar Warts	9
Morphea	6
Scleroderma	5
	273

VERRUCAE

There were 69 cases of verrucae in this group. They included 38 cases of verrucae vulgaris, 9 cases of verruca plana, 12 cases of plantar warts and 10 cases of filiform warts. In the multiple verruca vulgaris cases, 15 disappeared completely with no evidence of recurrence, 12 of the cases showed marked improvement, 4 cases showed slight response, and 7 cases grew worse under the treatment. Of the 9 cases of verruca plana, 4 of the cases responded completely to treatment; 5 of the cases showed slight improvement. In the 12 cases of plantar warts, 2 cases were treated with bistrimate alone and showed slight improvement clinically; they became less painful but the plantar warts did not disappear entirely under this form of therapy alone.

In the remaining 10 cases, bistrimate was used as an adjunct to radium therapy and peeling methods. When checked with control cases, the oral bismuth proved to shorten the duration of the treatment; and the percentage of recurrences was definitely lowered. The treatment of filiform warts was augumented by oral bismuth. In the 10 cases treated by various accepted methods, the use of bistrimate proved an excellent adjunct to these various methods.

LUPUS ERYTHEMATOSUS

Several workers have made contributions on the effect of bistrimate when used in lupus erythematosus. The new oral bismuth preparation seems to be very efficacious in the acute discoid type but to a lesser degree in the subacute discoid and chronic atrophic types of lupus erythematosus. Many of the patients with lupus erythematosus included in this study had been treated previously with parenteral bismuth therapy, without any apparent curative effect, but where oral bistrimate was substituted for parenteral bismuth preparations, the response was in many cases satisfactory and lasting. Most investigators reported uniformly good response in early cases of discoid lupus erythematosus (duration six months or less) but results in the more chronic cases of discoid lupus erythematosus varied somewhat.

The results we obtained in our series of 69 cases of lupus erythematosus seemed very encouraging.

CHART II

SUMMARY OF THE CASES OF LUPUS ERYTHEMATOSUS TREATED WITH BISTRIMATE

Type	Number of Cases	Clinical Response: Good to Excellent	Clinical Response: Fair Improved	Clinical Response: Unimproved Poor
Subacute Disseminated	3		1	2
Acute Discoid	54	22	18	14
Chronic Discoid	12	2	3	7

In none of the cases of the discoid type of lupus erythematosus did the patient become progressively worse under bistrimate therapy. However, in a few cases of subacute disseminated lupus erythematosus the patient seemed to become worse under oral bismuth therapy.

All of the cases included in this series have been given supportive therapy, such as vitamins, tonics, general, hygenic measures, and mild, topical applications. Topical therapy is not curative in lupus erythematosus; therefore, it cannot be considered as playing much much part in the results obtained. None of these cases received any gold injections. In our study the best results obtained in the lupus erythematosus group were in the acute discoid cases; in the subacute cases, the response was encouraging but less effective. In the chronic discoid type the results obtained were not as spectacular. In the chronic discoid variety there was radical scarring present after the lesions disappeared.

Of the three patients with subacute disseminated lupus erythematosus one showed marked improvement, but, as is well known, this disease is a serious one and an acute exacerbation may occur. Two of the three patients have shown no response or have become worse under the bistrimate therapy.

The patients received on the average of four tablets daily. Some received two tab-

lets three times daily, or a total of 450 mgms. of the drug daily and continuously. The average time during which the patients in this group received bistrmate tablets was three and one-half months. Some have required up to five and one-half months; in some of the patients the good response to the drug is still going on and in time may be classified as a clinical cure.

The number of cases of the disseminated type was so small that it would seem unwise to draw any conclusions in appraising the results of the drug in the treatment of such a serious disease and one accompanied with such a high degree of mortality.

VITILIGO

For some time we have used bismuth subsalicylate in the treatment of vitiligo, with varying results. The parenteral use of bismuth alone and in combination with gold and sodium thiosulphate injections intravenously has been employed. The response seemed to depend largely on the duration of the pigmentary disturbance and the age of the patient. Bistrimate tablets were substituted for the parenteral bismuth and the response was very gratifying. There were 56 cases included in a group in which bistrimate alone was used as an internal therapeutic measure. Twenty-nine of the 56 patients showed slight to marked improvement, as evidenced by minute deposits or islets of pigment appearing in most of the cases, after six to eight weeks of bistrimate therapy. Complete return of pigment was noted in 9 of the patients, after four to eight months of bistrimate therapy. The pigmentary deposits are continuing to appear in many of the patients in which there was any response shown at all. Since this condition is known to be very recalcitrant to therapy and by many is considered incurable, the seemingly long time required for complete recovery is not objectionable. An observation made in most patients with vitiligo, even in 18 which were classified as showing no response to bistrimate therapy, was the absence of new lesions. Bistrimate seemed to stop the progress of the depigmentary disturbance in nearly all of the patients treated.

In five of the patients treated, return of pigment began to be manifest after two to four weeks of bistrimate therapy. In a general observation the young and middle aged patients showed much better response to bistrimate than did the older individuals, particularly the women patients near or subsequent to menopause. It might then be stated that the younger the patients, the better the response to oral bismuth therapy in the treatment of vitiligo.

The time required in the treatment of most cases of vitiligo to obtain satisfactory results was longer than the time interval needed in treating acute discoid lupus erythematosus. The dosage used was one to two tablets of bistrimate three times daily; most of the patients tolerated the larger dose.

LICHEN PLANUS

Heavy metal therapy has long been employed for the treatment of lichen planus. Both bismuth and mercury have been used parenterally and have been accepted as a therapeutic measure of debatable value.

Because of the many advantages of oral bismuth over the parenteral form of bismuth, 39 patients with lichen planus were treated with oral bistrimate. Twenty-eight of these cases were acute, generalized lichen planus. Eighteen of these acute cases showed response within four and one-half months. All of the cases were extensive and generalized and the results were considered very satisfactory. Ten of the patients with acute generalized lichen planus did not respond to oral bismuth therapy. There were 11 cases of hypertrophic lichen planus in this group. Seven of these hypertrophic cases seemed to be unaffected by oral bismuth. All patients were given an ointment containing four to six per cent hydrarg. ammoniatum ointment with 6 per cent salicylic acid incorporated as a keratolytic agent.

A control series of 8 acute lichen planus cases, in which the same topical applications were used but with no heavy metal, showed very slight response, if any at all. Vitamin B complex, a laxative, and in cases where pruritis was intense, a mild sedative, were used in both series. Our results were

definitely better in the acute cases of lichen planus.

GRANULOMA ANNULARE

In the small series of 9 cases of granuloma annuare treated with bistrimate, the results were very satisfactory. In 5 of our patients almost entire disappearance of the lesions have occurred with bistrimate therapy in less than eight months' time. In 2 patients included in this series roentgen therapy was used and they responded no quicker than the other 3 who received only bistrimate. To confirm the diagnosis, biopsies were done on 7 of the 9 patients. In the other 2 patients a biopsy was not thought necessary to establish the diagnosis as they were both classical.

One of the patients who showed very rapid response to bistrimate therapy had multiple lesions of both forearms and dorsum of the hands. Five years ago this patient was seen with a few annular lesions of the forearms and was treated with unfiltered x-ray, with very little response. The patient was not seen for five years and at this time the biopsy was repeated, and on her return the eruption was extensive as described. She was put on bistrimate and treated with a small dose of unfiltered x-ray at monthly intervals for six months. In two months' time the lesions receded to a considerable degree and continued to recede until at the end of one year she was entirely clear of the lesions. One cannot help being impressed by the excellent results obtained in the treatment of granuloma annulare, with bistrimate.

SARCOIDOSIS

Eleven patients with cutaneous sarcoid infection of the Boeck's type were treated with bistrimate. Three of the cases were generalized in type, showing largely dispersed areas on the skin, as well as on the scalp, and generalized adenopathy with bone changes in the phalanges. Biopsies of skin confirmed the diagnosis in all cases and gland biopsies were also done. The response of these patients to bistrimate as an auxiliary measure to the usual routine therapeutic measures employed in treating this recalcitrant, chronic disease, has been surprisingly good. The response of these 3 extensive cases of sarcoidosis seemed to be quicker than in the few other cases of this disease of a comparable degree of severity seen by the author. No gold therapy was used in this small series. In fact, bistrimate was used as a substitute for gold and sodium thiosulphate. We have used parenteral bismuth in other cases of sarcoidosis alone or in combination with gold therapy, but the results seemed to be better when bistrimate alone was used in place of these other drugs. Five of the patients with sarcoidosis in this series have been under continuous bistrimate therapy for over two years without any untoward effects. No evidence of saturation with bistrimate has been noted in this group.

Eight cases of localized sarcoidosis, all of which were diagnosed microscopically as Boeck's sarcoid, were treated with bistrimate.

The response of most of these localized cases of sarcoidosis was slow, as is all therapy in this disease, but the results were encouraging, considering the recalcitrance of this chronic infection.

It is not too optimistic to assume that we have a definite adjunct to our therapeutic armamentarium for sorcoidosis.

SCLERODERMA AND MORPHEA

The interest in scleroderma and morphea began when Gross followed the suggestion of Stokes[7], that a parenteral bismuth compound be used in a morphea-like case which was being discussed at the meeting of the Philadelphia Dermatological Society.

Only 6 cases of morphea and 5 cases of generalized scleroderma treated with bistrimate, are included in this report. The results were very good in 6 of the patients but all cases showed a distinct degree of softening of the skin. No ulcerative lesions were present in any of these patients.

Gross has collected a large series of scleroderma and morphea cases which he has treated with bistrimate, with excellent results. In our original paper[1] on the study of bistrimate, the most uniformly successful results among the nonspecific inflammatory diseases treated with bistrimate were among the scleroderma and morphea groups. Stryker, Tweedal and O'Con-

ner[8] reported 2 cases of diffuse scleroderma which were symptomatically benefitted by oral bistrimate.

REACTIONS

The reactions encountered with bistrimate therapy in our series are very few and of mild nature. These findings are contrary to a few reports in the literature, although they are on a small group of cases.

The chief complaint which we observed and which occurred in many patients was "sore gums". This form of gingivitis is not of a severe type and responded to simple hygienic measures. It was not necessary to discontinue the bistrimate therapy in many cases. Aerating mouth washes and riboflavin controlled all of the conditions.

Many of the cases of chronic dermatoses, requiring a longer period of bistrimate therapy, developed a bismuth line of the gums. It was a bluish gray color but caused no serious complications. It is not the severe type of gingivitis so frequently seen in patients treated with some of the internal mercurial preparations, or with parenteral bismuth.

No renal damage was elicited by frequent urinalysis. No hepatic complications were encountered, though in some of the patients receiving prolonged bistrimate therapy, blood chemistry examinations were made at monthly intervals.

Severe stomatitis occurred in one patient having an acute lupus erythematosus, after taking four bistrimate tablets. She gave no allergic history but did give a history of idiosyncracy to numerous drugs.

A few patients complained of gastric pains of a vague type which required no permanent cessation of bistrimate therapy. A mild gastric intestinal upset observed frequently was not considered as a contraindication to the oral bismuth therapy. A few cases of stomatitis were seen which warranted discontinuation of the drug, but most of the patients with stomatitis were able to resume bistrimate therapy when the dosage was reduced.

Trigeminal neuralgia[9] and tinnitus are reported as a complication of bistrimate therapy. Only a few cases of trigeminal neuralgia were noted in our series and they were of a mild type and did not require permanent discontinuation of therapy.

Anorexia was encountered in a small number of patients but was of a temporary nature. In most of the mild reactions, reductions of the dosage for a day or two rectified the complications.

In 1 case treated, by one of my associates, the patient developed an exfoliative dermatitis after a short course of bistrimate therapy. The condition was considered to be due to the oral bismuth. No other severe complications were encountered in the study. Blood counts were done frequently on the patients from my private practice and only occasional transient changes were seen in the blood picture while on bistrimate therapy. A transient leukopenia has been reported. Sawicky attributed it to bistrimate.

Neither diarrhea nor constipation were encountered in more than a normal rate while on bistrimate.

SUMMARY

The results of a study of certain nonspecific dermatoses, some of unknown etiology, treated with bistrimate, are reported.

It is a continuation of the study previously reported by Gross[2] and the author[1], but in this report no cases of syphilis are included. While the investigative work on bistrimate in that disease is continuing, it is thought that bistrimate is of sufficient therapeutic value in treating certain nonsyphilitic dermatoses to warrant a report of its use in these cutaneous diseases. No cases reported in the original paper are included in this survey.

Most of the varieties of dermatoses considered in this report were in the preliminary report heretofore referred to. There are a few dermatoses such as vitiligo, and sarcoidosis that were not included in the original paper.

The encouraging results obtained in the granuloma annulare group were very impressive.

The response of acute discoid lupus erythematosus to bistrimate therapy seems to establish this drug as a definite adjunct to

the list of common therapeutic measures generally used in treating this troublesome skin condition. A few of the dermatoses considered were not of adequate number, nor was the time during which they were treated sufficient to make any deductions of much value.

Perhaps the most impressive features, I might even say surprising observations, occurred in the response of the granuloma annulare, scleroderma, and sarcoidosis cases. The lupus erythematosus group continued to respond in a most favorable manner, particularly in the acute cases.

A small series of a few of nonspecific inflammatory dermatoses have been treated with bistrimate but the number of cases of each disease is not large enough, or the treatment with bistrimate not long enough to include in this report the observations and results from these small groups.

CONCLUSION

Bistrimate was found to be of great therapeutic value in treating certain inflammatory dermatoses, and in some dermatoses not accompanied by an inflammatory reaction, when given in dosages of three to six tablets daily, preferably after meals. Each tablet contained the equivalent of 75 mgms. of metallic bismuth.

From all appearances, the drug seems to be an excellent adjunct to our dermatologic armamentarium, particularly when used as an auxiliary or supplementary measure.

The relatively low toxicity of bistrimate, the excellent tolerance to this drug, the ease of administration, the infrequency of even mild complications, and the proved balance of the rate of absorption and excretion, seem to justify its use in the types of dermatoses in this survey.

The uncertain control the physician has of the patient when oral medications are used in preference to intramuscular and intravenous drugs, is well recognized, but if one doubts the integrity of his patient to that extent, then all oral medications are to be relegated to a very dubious level.

The results being obtained in the continuance of bistrimate tablets in the various types of syphilis are most encouraging, particularly in late cutaneous and asymptomatic syphilis. Since this survey comprises part of the original investigations of this oral form of bismuth, we have naturally included observations on a number of dermatoses that were eventually discarded from our survey as being of too little value. As new dermatoses are added to the group we are encouraged by the response to this form of bismuth in some of the nonspecific conditions, such as granuloma annulare and sarcoidosis.

The author is cognizant of the danger of over enthusiasm which is often found when any new drug or therapeutic measure is introduced. This drug is not presented as a panacea, nor does it approach such a standard, but when sufficient usage has enabled us to permit the pendulum of judicious therapy to obtain its proper orbit, we feel bistrimate is a safe and effective therapeutic aid and a great help to the specialty of dermatology and syphilogy, in many of our recalcitrant dermatoses.

Sodium bismuth triglycollamate (bistrimate) by mouth appears to be at least as effective as parenteral bismuth therapy (bismuth subsalicylate) in the treatment of some of the inflammatory dermatoses, as listed in this paper. When we consider the convenience of the oral form of therapy and the comparative safety of the oral route over the parenteral form, then the use of the drug seems justified in dermatoses where bismuth is indicated.

REFERENCES

1. Howles, J. K.: South. M. J., 41:1033-1041, Nov. 1948.

2. Gross, Elmer and Howles, J. K.: Read before the Section of Dermatologists at the American Medical Associating Meeting, Atlantic City, New Jersey, June 12, 1947.

3. Sawicky, H. H.: J. Invest. Dermat. 9:159, (Sept.) 1947.

4. Wright, C. and Gross, E. R.: Arch. Dermat. & Syph. 55:862, (June) 1947.

5. Pascher, F., Sawicky, H. H., Silverberg, M. G., and Emmet, R.: J. Invest. Dermat., 10:441, (June) 1948.

6. Lehman, R. A. and Sproull, R. C.: J. Am. Pharm. A., 31:190, 1942.

7. Stokes, J.: Society Transactions. Arch. Dermat. and Syph., 53:66, (Jan.) 1946.

8. Stryker, Harold V.; Tweedal, Daniel C.; and O'Connor, W. B.: J. Invest. Dermat., 2:399, (Dec.) 1948.

9. Noun, Maurice H. and Greenhill, S.: Arch. Dermat. & Syphil. 59:347, (March) 1949.

10. DeGraff, A. C. and Associates, Department of Therapeutics, New York University College of Medicine and the Third (New York University) Division of Bellevue Hospital.

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LET US TAKE STOCK

Sixteen years ago a program of socialistic government and economy was initiated by legislative action. Seven years ago a plan of state medicine was proposed and seriously advocated as part of such a program. Some of the results of these policies are now manifest. Former President Hoover said in effect that we were now traveling the broad highway to statism. Former Secretary of State Byrnes said that we were faced with the gradual emergence of the "welfare state." Foreign Secretary Ernest Bevin of Britain declared recently that "the United States is as much of a welfare state as we are."

In the face of such a situation let us take stock. Our dictionary definition of welfare work is "organized community or corporate efforts for social betterment of a class or group." Let us see then to what extent we are a welfare state. The British program consists of seven chief components. These are food subsidies, low rent housing (including rent control), unemployment compensation, cheap milk free to school children, pensions and national health service, and certain family allowances.

The American program consists of seven similar projects. These are food subsidies, low rent housing(including rent control), unemployment compensation, free school lunches, pensions, and various health activities and public assistance of many types.

The total cost of the British welfare plan is $5,515,000,000 or $51 per capita. The cost of our activities in this field is $7,724,000,000 or $110 per capita. This then is conclusive proof that we are a welfare state; that the observations of the eminent statesmen were correct, and that the social planners have insidiously introduced in sixteen years a new type of government.

The people of Britain have been lured into accepting and then demanding this sort of social order. The proof here lies in the fact that it is admitted that whichever party wins the coming general election in England it will not undertake to reduce the welfare expenditures materially. This is considered a political necessity in spite of that fact that their income tax starts at 45 per cent and the recent crises show that the country is in a state of economic stagnation.

When we take stock of our position, therefore, we must realize that we also have been lured into becoming a welfare state; that the social planners advocate further extension in compulsory sickness insurance, and more recently in the atrocious Social Security Bill, HR 6000. This bill if made into law will constitute a great threat to our economic liberty and may become the means of introducing state medicine by the side door. The proposed Social Security bill would cost from $16,000,000,000 to $24,000,000,000 annually by 1960. Under such conditions, and with this added to existing budgets, one-third of the national income

would be consumed in taxes. Consequent upon such plans would be freezing out of insurance companies and a gradual drying-up of "risk capital."

In discussing the unwillingness of physicians to be taken over by politicians, we could do well to speak on the vicious trend from the welfare state to the police state. The public should realize that there is a fallacy in one-half of the population carrying the other half until they both drop.

In a different age it was taught that the citizens should support the government, and now we are beset with the idea that the government should support the citizens.

We are told bythe national authorities of the Community Chest that four out of every ten families in the metropolitan areas are served in some manner by the Community Chests—in the most prosperous year of the richest country in the world.

Our situation then is one in which our battle against socialized medicine is only a part of a larger battle against the trend of socialism. It is gratifying in recent months to see this stated frankly in high places, and, in accordance with the old dictum that truth hurts, it is interesting to see socialism disclaimed. Now, more than ever, organized medicine should work with the stable elements of the body politic and defeat the plans of an organized minority.

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ORGANIZATION SECTION

The Executive Committee dedicates this section to the members of the Louisiana State Medical Society, feeling that a proper discussion of salient issues will contribute to the understanding and fortification of our Society.
An informed profession should be a wise one.

1950 ANNUAL MEETING

The Seventieth Annual Meeting of the State Society will be held in Baton Rouge, April 24-26, 1950. Headquarters for the meeting will be at the Heidelberg Hotel and arrangements have been made for adequate meeting rooms, scientific and technical exhibit space, and accommodations for members and guests in attendance. Dr. U. S. Hargrove is general chairman of the Committee on Arrangements and Dr. Arthur D. Long is serving as co-chairman of this committee. Assisting these doctors will be the following chairmen of various subcommittees: Dr. Lester J. Williams, Advisory; Dr. Henry C. Hatcher, Budget; Dr. J. Webb McGehee, President's Ball; Dr. William O. Vennard, Golf Tournament; Dr. Edward G. Cailleteaux, Hotel Reservations; Dr. Claude S. McConnell, Decorations; Dr. Oswald W. Cosby, Lanterns and Movies; Dr. Clifton T. Morris, Publicity; Dr. Leonard H. Stander, Scientific Exhibits; Dr. Charles H. Mosely, Jr., Commercial Exhibits; Dr. W. Shewen Slaughter, Transportation; Dr. Arthur D. Long, Woman's Auxiliary; Dr. William K. Irwin, Registration; Dr. Thomas Y. Gladney, Communications; Dr. H. Guy Riche, Jr., Signs; Dr. Joseph J. Noto, Luncheons; Dr. Moss M. Bannerman, Meeting Rooms. It is suggested that members refer to this list of committee chairmen when information or assistance is needed in connection with various phases of the meeting.

Dr. Donovan C. Browne, of New Orleans, has ably served as General Chairman of the scientific program for recent meetings and the president of the State Society, Dr. Edwin H. Lawson has appointed him to again serve in this capacity for the 1950 meeting. In addition, Dr. Lawson has appointed the following members to serve as chairmen of the scientific sections: Dr. Henry D. Ogden, Allergy; Dr. Spears Randall, Bacteriology and Pathology; Dr. Marion E. Kopfler, Dermatology; Dr. L. W. Alexander, Ear, Nose and Throat; Dr. George M. Haik, Eye; Dr. Jack R. Jones, Gynecology; Dr. Sam Hobson, Medicine; Dr. T. A. Watters, Neuropsychiatry; Dr. Eugene H. Countiss, Obstetrics; Dr. Jack E. Strange, Pediatrics; Dr. Owen F. Agee, Public Health; Dr. Howard Mahorner, Surgery; Dr. DeWitt T. Milam, Urology, Dr. L. J. Bristow, Jr., Radiology. Appointments

have not yet been made for the sections on gastro-enterology and orthopedics; however, these will be made within a short time. Dr. Harold M. Horack is in charge of the program for the Louisiana Heart Association session which will be held at the time of the State Society meeting and Dr. D. B. Barber, President of the Louisiana Branch of the American Academy of General Practice, will appoint a member to arrange the program for the section on general practice.

Booths for technical exhibits will be installed in the Capital Room of the hotel and also on the mezzanine floor. The capital room is on the highest floor and adjacent to the meeting room of the House of Delegates and general scientific sessions. Meeting rooms for the specialty groups will be located on the mezzanine floor and the scientific exhibits will probably be located on this floor also.

It can be understood from the above that much has already been done in preparation for this meeting and it is hoped that every member will make every possible effort to be present.

CANCER COMMITTEE ACTIVITY

Currently each week doctors in the eight districts throughout the state are receiving invitations to visit the Tulane and LSU Cancer Detection Clinics. This is a splendid opportunity for the members of the medical profession to observe the best in clinical examination and to keep abreast of the cancer problem in the progress of scientific medicine. Responsibility to patients requires that doctors keep informed of the advances in essential phases of diagnosis. The doctor's duty is to achieve a cancer-consciousness which will make him use every means to rule out possibility of cancer. We are confident that all who possibly can will avail themselves of this opportunity to widen their knowledge.

The Tulane clinic is held each Wednesday and Friday afternoon at 12:30. Doctors attending are requested to report to Miss Weber's office on the first floor of the Medical School, 1430 Tulane Avenue.

At 10:30 a. m. each Wednesday there is a surgery conference and at 3:00 p. m. a cancer conference. The latter is held in the Delgado Amphitheater. You are cordially invited to attend these sessions while observing the work in the detection clinic.

The LSU Detection Clinic is held on the eighth floor of the LSU School of Medicine, 1542 Tulane Avenue, each Monday and Wednesday afternoon, beginning at 12:30.

There has been provided in the budget an appropriation which will allow each doctor who accepts this opportunity reimburse-equivalent to the cost of round trip transportation by rail from his home. If reimbursement is desired request should be submitted to Dr. John G. Snelling, Chairman Cancer Committee, Ouachita Bank Building, Monroe.

John G. Snelling, M. D., Chairman,
Committee on Cancer.

LOUISIANA STATE MEDICAL SOCIETY NEWS

CALENDAR

PARISH AND DISTRICT MEDICAL SOCIETY MEETINGS

Society	Date	Place
East Baton Rouge	Second Wednesday of every month	Baton Rouge
Morehouse	Second Tuesday of every month	Bastrop
Natchitoches	Second Tuesday of every month	
Orleans	Second Monday of every month	New Orleans
Ouachita	First Thursday of every month	Monroe
Rapides	First Monday of every month	Alexandria
Sabine	First Wednesday of every month	
Second District	Third Thursday of every month	
Shreveport	First Tuesday of every month	Shreveport
Vernon	First Thursday of every month	

INDUSTRIAL HEALTH CONGRESS

The Council on Industrial Health will hold its Tenth Annual Congress on Industrial Health at the Roosevelt Hotel in New York City, February 20 and 21, 1950.

NEWS ITEM

Dr. Lucien A. LeDoux attended the Annual Meeting of Abdominal Surgeons, Gynecologists and Obstetricians recently held in Hot Springs, Virginia.

GET INTO POLITICS TO BEAT SOCIAL MEDICINE, ARENDS TELLS DOCTORS

No matter what the Washington planners say, the compulsory sickness insurance proposal now before Congress means nationalization of American medicine down to the last bottle of aspirin," Representative L. C. Arends (Representative, Ill.) of Melvin, Illinois, told the Illinois State Medical Society (Sunday, September 11).

Representative Arends, who is the Republican whip of the lower house, was keynote speaker at an all-day conference called by the Society in the LaSalle Hotel to discuss the "big push" the administration is expected to make this winter to put over the compulsory sickness insurance proposals embodied in S. 1679. Representatives of most of the 91 county medical societies in Illinois were present together with spokesmen for many other groups opposing socialized medicine. Percy E. Hopkins, M. D., of Chicago was in charge of the meeting, while Walter Stevenson, M. D., of Quincy, president of the Ilinois State Medical Society, acted as chairman.

Representative Arends called on the medical and other professions represented to get into politics actively and aggressively as the only way to disinfect the national government of the socialist contagion.

"When an American citizen is sick or infirm," Representative Arends told the medical men, "he wants to consult a doctor of medicine, not a doctor of philosophy in the Social Security Board, or a doctor of law in the Federal Security Administration, or yet a doctor of political science, or a doctor of civil administration.

SIXTH DISTRICT MEDICAL SOCIETY

The spring meeting of the Sixth District Medical Society was held at Pallud's Restaurant, Baton Rouge on Tuesday, April 26, 1949 at 8:00 p. m.

The meeting was called to order by the President, Dr. Guy Riche, Sr., Baton Rouge.

The regular order of business was followed. The following physicians were elected as officers for the incoming year: President—Dr. J. DeLoach Thames, Hammond; Secretary—Dr. Burl B. Lane, Jr., Zachary; Treasurer—Dr. Cecil Lorio, Baton Rouge; Vice-Presidents: Ascension—Dr. D. C. Brumfield, Darrow; East Feliciana—Dr. E. M. Robards, Jackson; East Baton Rouge—Dr. Charles McVea, Baton Rouge; Iberville—Dr. Eugene Holloway, Plaquemine; Livingston—Dr. M. Williams, Denham Springs; Tangipahoa—Dr. M. B. Small, Kentwood; East Feliciana—Dr. Glen Smith, Jackson; St. Tammany—Dr. Carl Young, Covington; Washington—Dr. William S. Harrell, Bogalusa; West Baton Rouge — Dr. George Thomas — Port Allen; West Feliciana—Dr. C. J. Wise, Angola; Pointe Coupee—Dr. F. F. Rougon, New Roads.

Dr. M. D. Hargrove of Shreveport gave an enlightening talk entitled "Our Society" in which he discussed the Murray, Wagner, Dingle Bill.

Dr. J. Ralph Phillips of Baton Rouge gave a very interesting talk on "Emergency Treatment of Eye, Ear, Nose and Throat Conditions by the General Practitioner."

An invitation by the Superintendent, Dr. Glenn J. Smith, and Dr. E. M. Robards to hold the next meeting of the Society at the East Louisiana Hospital at Jackson was accepted.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The annual meeting of the Board was held in Chicago, Illinois, May 8-14, 1949, at which time 236 candidates were certified.

New bulletins, incorporating changes made at the recent meeting, are now available for distribution upon application and give details of all new regulations.

The next scheduled examination (Part I), written examination and review of case histories, for all candidates will be held in various cities of the United States and Canada on Friday, February 3, 1950. Application may be made until November 5, 1949. Application forms and bulletins are sent upon request.

WOMAN'S AUXILIARY TO THE LOUISIANA ACADEMY OF GENERAL PRACTICE

With the records of the second annual convention of the Woman's Auxiliary to the Louisiana Academy of General Practice filed, and in order, preparations are now being made for a third meeting to be held in Alexandria, Sunday and Monday, December 11-12, 1949. The previous date of November 12 conflicted with the Southern Medical Association Convention meeting in Cincinnati to be held at that time, and due to hotel reservations already recorded, it was necessary to change the dates for the Alexandria meeting. There will be a definite schedule of plans sent out to the ladies in due time but mark these dates on your calendar.

It has been decided that the interests of the general practitioner will be served more completely if the Academy holds a scientific assembly in the fall, as the Louisiana State Medical Society holds its meetings in the spring. The meetings should in no way conflict, for it is the aim of the Auxiliary to work for the good of both the State Society and the Academy of General Practice.

The president of the Auxiliary, Mrs. D. B. Barber, has contacted the National Board of Directors of the American Academy of General Practice and requested that a positive and active decision be made at their September meeting in Kansas City, as to whether the Louisiana Auxiliary can lay the ground work in organization of a national auxiliary to the Academy, before the National Assembly meets in St. Louis in February. You may be

assured that our own vice-president of the National Academy, Dr. J. P. Sanders, will do everything within his power to convince his board that now is the time to organize an auxiliary. We shall await their decision and if it is in the affirmative plans will be made at once to carry on the work for organization. Come to the Alexandria assembly and hear all about this from your president, Mrs. Barber. Congratulations have come from every national and state officer on the fine enthusiasm of the Women's Auxiliary to the Louisiana Academy to promote the general practice program over this state. We, in Louisiana should be proud that we organized the first auxiliary of its kind in the nation.

It is the aim of both Academy and Auxiliary members to have it well understood that the "baby auxiliary," as we are referred to, will in no possible way interfere with established groups, nor at any time overstep the bounds of activity in any way but to serve the particular interest of the general practitioner. New Orleans ladies are particularly asked to contact Mrs. Bruno Mancuso at Franklin 8401, to arrange for a pre-convention meeting in October.

Your state president, Dean Barber, will notify her executive officers, and auxiliary members in due time of the activities for the ladies during the Assembly. Plans are being formulated but since no definite program has yet been assembled, each member will be notified, personally by the president. Keep your fingers crossed for the decision at the national board meeting this month, and come to your state scientific meeting in Alexandria with a determined spirit to make this FIRST AUXILIARY a SUCCESSFUL ONE. Other leading spirits in the venture are Mrs. Wiginton, the beloved first president, and Mrs. Feldner, president-elect of the group.

The men have advanced the slogan, "Every member bring a member". The women shall say, "Contact the wife of another member and ask her to go to the December convention." The paths that lie ahead are new and untrodden but with careful planning and cooperation from all we may feel assured of a successful meeting at both Alexandria and St. Louis.

Mazie Adkins Guidry,
Publicity Chairman.

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BOOK REVIEWS

Practical Nurse: By Dorothy Deming, R. N.. N. Y. Commonwealth Fund, 1947, pp. 370. Price, $3.00.

This "presents for the first time in book form, a summary of past experiences and current practices in practical nursing, as well as best thinking on how to develop a new and desirable kind of practical nurse to serve as a partner for the registered nurse," and will serve as an excellent guide in organizing a program for practical nurses.

Practical nurses are badly needed to fill the gap in nursing which has resulted from the many opportunities occurring in the field of business and industry for competent women; also the advancement in professional nursing has taken many nurses from the bedside.

Miss Deming has more than adequately covered preparation, supervision, legal control, and distribution of practical nurses. Chapters 13, 14 and 15 will aid greatly in establishing schools of practical nursing, setting up curricula for these schools and supervision of graduates of such schools.

After reviewing this book, one is well convinced that it has fulfilled its urgent and fundamental reason for being, "the conviction that patients need and deserve the best practical nursing care they can get".

ROSE H. LINDAUER, R. N.

Treatment in General Practice: By Harry Beckman, M. D., 6th Ed., Philadelphia, W. B. Saunders Co., 1948, pp. 1159. Price, $11.50.

This is a sixth edition. The reveiwer has on past occasions stated that when a book has reached into numerous editions it hardly needs any additional critical comments. Yet one cannot resist the thought that the rapid pace of medical advance makes a new edition dated even as it is coming off the press. The author states that "The revision for this sixth edition . . . has been as completely unsparing as progress itself is ruthless." Several new subjects have been included for the first time.

I. L. ROBBINS, M. D.

The Technique of Pulmonary Resection: By Richard H. Overholt and Lazaro Langer, pp. 195. Charles C. Thomas, Springfield, Ill. Price, $8.00.

The monograph by Overholt and Langer is excellently done. It is well illustrated and describes in minute detail the preparation of patients who are to undergo resections of the lung or portions of it. Considerable attention is given to the use of a face-down position and the use of local anesthesia, both of which Dr. Overholt has popularized. Minute description of the isolation and handling

of the individual hilar structures in the performance of pneumonectomies, lobectomies, and segmental resections are included. A considerable amount of space is given to consideration of surgical anatomy of the intrapulmonary and hilar structures. Illustrations are colored, which facilitates their being understood. The technic of segmental resection, which has been popularized by Overholt is described in detail. Postoperative management and the indications for postresection thoracoplasty are also given. The monograph is a real contribution and should be in the library of every individual who contemplates doing thoracic surgery.

ALTON OCHSNER, M. D.

Medical Etymology: The History and Derivation of Medical Terms for Students of Medicine, Dentistry and Nursing: By O. H. Perry Pepper, M. D. Philadelphia, W. B. Saunders Co., 1949, pp. 263. Price, $3.00.

In this small and inexpensive volume, the difficult problem of medical terminology is presented in a manner so reasonable that new workers in the field of medicine can understand and remember the maze of nomenclature. An explanation of the background of medical terminology is followed by explanations of the use and meaning of common prefixes, suffixes, compounds, and transliterations. We are told how eponyms have become a part of medical language, in the association of proper names with conditions and subjects; and of onomatopoetic words, which by their very sound are descriptive.

In each of the preclinical and clinical subjects, lists of words with derivation are presented in such a manner as to make the term itself descriptive and full of meaning. An alphabetic index of the 4,000 principal medical terms enhances the usefulness of the book as a practical tool.

Not the least attractive feature of the book is an inimitable touch of humor which sugar coats the pill. This volume should be a must for every student of medicine, nursing, and dentistry.

MARY LOUISE MARSHALL.

Geriatric Medicine: The Care of the Aging and the Aged: Edited by Edward J. Stieglitz, M. D., M. S., F. A. C. P. 2nd ed. Philadelphia, W. B. Saunders Co., 1949, pp. 773, illus.

The fact that this book, first written during World War II, is now in a revised second edition bears witness not only to its readability and wealth of information, but also to the increasing importance of geriatrics. The individual past the age of forty is discussed system by system, with well known specialists taking over in their respective fields. Due attention is paid to the foundation and principles of geriatric medicine as a whole. It is an exhaustive study, and may well serve as an excellent reference volume for any and all in the field of medicine.

C. BARRETT KENNEDY, M. D.

How to Become a Doctor: By George R. Moon, A. B., M. A. Philadelphia, The Blakiston Co., 1949, pp. 131, illus. Price, $2.00.

The author states this to be a "complete guide." He discusses in an informed manner the quantitative requirements for admission to medical school. He considers the selection of a school and the many problems of the student, male and female, from the beginning to the end of the collegiate career. Since the author is the "Examiner and Recorder of the University of Illinois Colleges of Medicine, Dentistry and Pharmacy," it follows that out of a long experience with students and their problems he has accumulated a fund of information that should be invaluable to those hankering after a professional career and its successful accomplishment.

I. L. ROBBINS, M. D.

PUBLICATIONS RECEIVED

Grune & Stratton, Inc., New York: Early Carcinoma of the Uterine Cervix, by Hansjakob Wespi, M. D.

W. B. Saunders Company, Philadelphia: Clinical Biochemistry,, by Abraham Cantarow, M. D., and Max Trumper, Ph. D. Fundamentals of Otolaryngology, by Lawrence R. Boies, M. D. Operations of General Surgery, by Thomas G. Orr., M. D., 2nd Editon.

Charles C. Thomas, Springfield, Illinois: Pollen-Slide Studies, by Grafton Tyler, M. D., F. A. C. P.